

Durham Research Online

Deposited in DRO:

27 March 2017

Version of attached file:

Accepted Version

Peer-review status of attached file:

Peer-reviewed

Citation for published item:

Berry, David J. and Steed, Jonathan W. (2017) 'Pharmaceutical cocrystals, salts and multicomponent systems ; intermolecular interactions and property based design.', *Advanced drug delivery reviews.*, 117 . pp. 3-24.

Further information on publisher's website:

<https://doi.org/10.1016/j.addr.2017.03.003>

Publisher's copyright statement:

© 2017 This manuscript version is made available under the CC-BY-NC-ND 4.0 license
<http://creativecommons.org/licenses/by-nc-nd/4.0/>

Additional information:

Use policy

The full-text may be used and/or reproduced, and given to third parties in any format or medium, without prior permission or charge, for personal research or study, educational, or not-for-profit purposes provided that:

- a full bibliographic reference is made to the original source
- a [link](#) is made to the metadata record in DRO
- the full-text is not changed in any way

The full-text must not be sold in any format or medium without the formal permission of the copyright holders.

Please consult the [full DRO policy](#) for further details.

Accepted Manuscript

Pharmaceutical cocrystals, salts and multicomponent systems; intermolecular interactions and property based design

David J. Berry, Jonathan W. Steed

PII: S0169-409X(17)30033-9
DOI: doi:[10.1016/j.addr.2017.03.003](https://doi.org/10.1016/j.addr.2017.03.003)
Reference: ADR 13093

To appear in: *Advanced Drug Delivery Reviews*

Received date: 18 November 2016
Revised date: 20 March 2017
Accepted date: 21 March 2017



Please cite this article as: David J. Berry, Jonathan W. Steed, Pharmaceutical cocrystals, salts and multicomponent systems; intermolecular interactions and property based design, *Advanced Drug Delivery Reviews* (2017), doi:[10.1016/j.addr.2017.03.003](https://doi.org/10.1016/j.addr.2017.03.003)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Pharmaceutical cocrystals, salts and multicomponent systems; intermolecular interactions and property based design

David J. Berry^{a*} and Jonathan W. Steed^b

a. Durham University, Division of Pharmacy, Queen's Campus, Stockton on Tees, TS17 6BH.

b. Department of Chemistry, Durham University, University Science Laboratories, South Road, Durham, DH1 3LE.

* Correspondence. e-mail: d.j.berry@durham.ac.uk Telephone: 01913 340817

Abstract

As small molecule drugs become harder to develop and less cost effective for patient use, efficient strategies for their property improvement become increasingly important to global health initiatives. Improvements in the physical properties of Active Pharmaceutical Ingredients (APIs), without changes in the covalent chemistry, have long been possible through the application of binary component solids. This was first achieved through the use of pharmaceutical salts, within the last 10-15 years with cocrystals and more recently coamorphous systems have also been consciously applied to this problem. In order to rationally discover the best multicomponent phase for drug development, intermolecular interactions need to be considered at all stages of the process. This review highlights the current thinking in this area and the state of the art in: pharmaceutical multicomponent phase design, the intermolecular interactions in these phases, the implications of these interactions on the material properties and the pharmacokinetics in a patient.

Key words

Pharmaceutical; Cocrystal; Salt; Intermolecular interactions; multicomponent crystals; Physicochemical properties; Bioavailability; Pharmacokinetics

1. Introduction

In the making of new medicines, it is important to optimise and control the quantity of an active drug which is delivered to the body, organ system, or tissue in question. Appropriate quality is achieved by strict control of the manufacturing route of the medicine, to meet its designated attributes, and the solid state chemistry of the drug molecule. This is done in order to ensure reproducible delivery of the drug to the right place at the right time to treat the disease. Alterations to the solid-state chemistry of drug molecules are common within the pharmaceutical industry as they enable modification of the physical properties of a drug, without changing the pharmacology of the active pharmaceutical ingredient (API) through modification of covalent bonds. Addition of second components to alter the APIs physical chemistry has been commonplace within the pharmaceutical industry for well over a quarter of a century in the form of pharmaceutical salts.[1] More recently, i.e. for around a decade,[2] it has also been common practice to include pharmaceutical cocrystals in the search for the optimum properties.[3-7] There have been many excellent reviews on the intermolecular interactions,[8] growth,[9] manufacture[10] and utility of cocrystals in this time,[11-13] along with significant advances to accompany them. There has been seeming reticence within the industry to turn the potential of cocrystals into products however. This issue has been partially blamed on a number of key perceived problems: regulatory uncertainty, problems with manufacture at scale and a lack of *in vivo* confirmation of the promise of these systems in the lab.[14] This review will address these points from the perspectives of the intermolecular interactions within these phases, their properties pertinent to

manufacture and their *in vivo* pharmacokinetics. Although not the focus of this review it is of note that recently the regulatory opinion of cocrystals has changed in the eyes of the FDA.[15] It is also important that the EMA[16] see the utility of these phases as their defining trait. With this in mind this review will focus on the following areas; intermolecular interactions, their implications on design towards robust manufacturing and their pharmacokinetics.

2. Intermolecular interactions in multicomponent crystals

2.1 Classification of multicomponent crystals

In the pharmaceutical context the basis of the utility of cocrystals and salts lies in the alterations they impart on the intermolecular interactions within the crystalline state and their potential to change *in vivo* solution behaviour through altered dissolution. Both cocrystals and salts have been seen to improve many manufacturing and biopharmaceutical properties within API materials, so knowledge of which characteristics to seek, using what chemical design strategy, is of great utility to the pharmaceutical industry and the patients it serves. It is commonly accepted that the bonding behaviours within salts and cocrystals lie along similar, though different, chemistry, but a specific tension is added within the confines of the pharmaceutical sector due to regulatory necessity. It has been suggested that cocrystals and salts offer new intellectual property opportunities.[17] Filing a patent requires some degree of definition of the disclosed phase however, as does the need to submit information about a new phase to regulatory agencies.[15, 16] This inherently drives an agenda which is sometimes more prescriptive, in terms of defining the nature of the phase, than the chemistry which controls it. Initially there was reticence to see salts and cocrystals as part of the same continuum,[18] but that has changed over the last decade as more data has emerged. Recently a Venn diagram approach has been proposed by de Gelder and co-workers to describe the differing phases and can be seen in Figure 1 (although the solid / liquid at 293.15 K, 10^5 Pa distinction between solvents and cocrystals represents a chemically arbitrary division).[19]

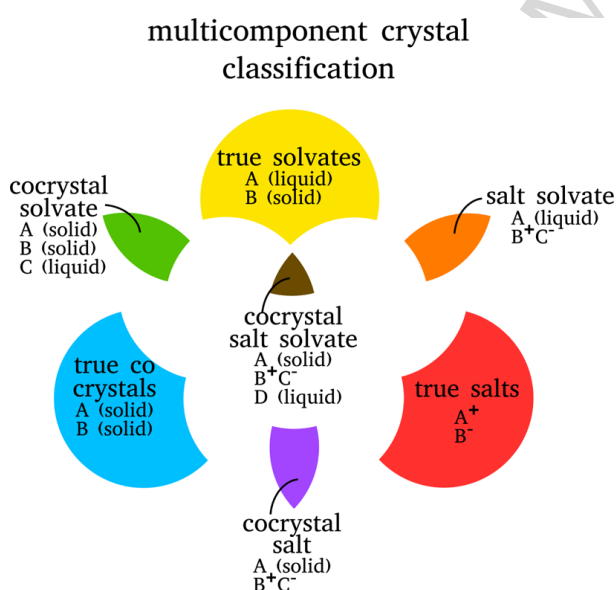


Figure 1. de Gelder and co-workers' Proposed classification system for pharmaceutical solid forms. From reference [19] with permission.

This depiction of bonding behaviours is a progression from the cartoon depiction of the solid form chemistry that has previously been used to describe these phases[12]. A version of such a cartoon can be seen in Figure 2. Here it is also evident that significant crossover is possible within cocrystal and salts. As it is clear that understanding the molecular level architectures within API phases are essential for appropriate form designation, section 2.2 will focus on examples of the relevant interactions. It also follows that without discovery of novel phases there is nothing to define, so this section will also deal with molecular level design strategies for the discovery of new drug phases (section 2.3) before discussion of property based design.

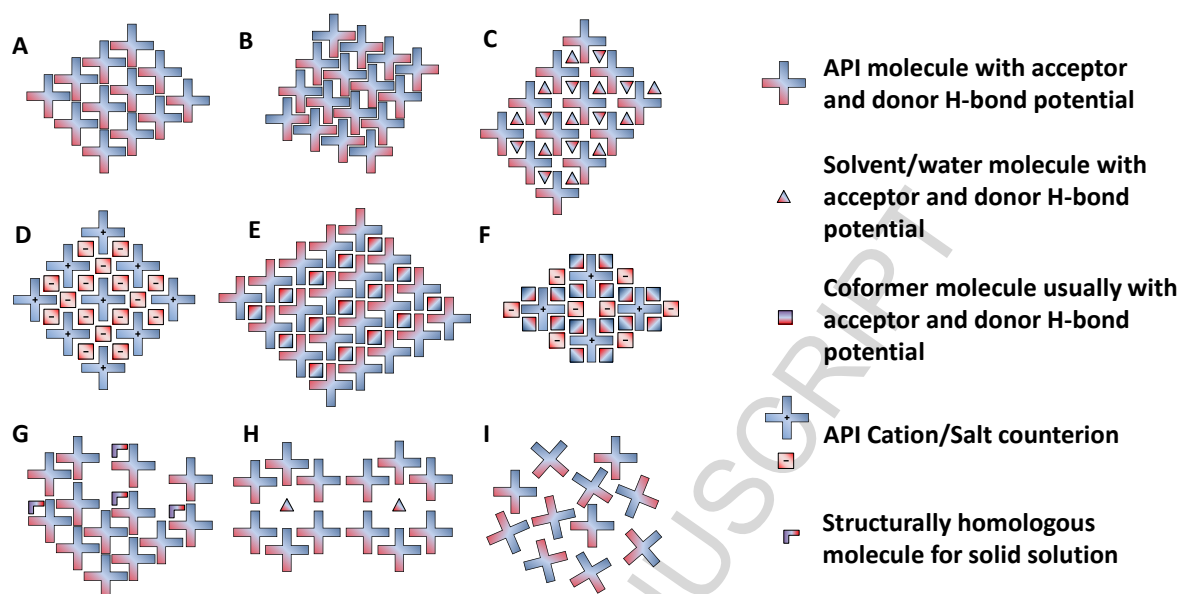


Figure 2. Possible form options for an API. **A** and **B** are polymorphs of the API (forms **C** to **H** are also potentially capable of forming polymorphs), **C** is a stoichiometric solvate/hydrate (can possess charge), **D** a classic salt, **E** a molecular cocrystal (conceptually identical to **C**), **F** an ionic cocrystal, **G** is a solid solution (mixed crystal), **H** is a potentially non-stoichiometric inclusion compound e.g. a channel hydrate and **I** is an amorphous form of the pure API, there is also potential to make forms **D** to **F** amorphous (Adapted from reference[12]).

2.2 Understanding Intermolecular interactions within salts and cocrystals

In order for any multicomponent crystal to form there must be some kind of interaction between the molecules or ions that make up the crystal. For the system to be thought of as multi-component (*i.e.* a cocrystal or salt of any of the types shown in Figure 2 C to H) such interactions are of a non-covalent and hence supramolecular type. While the energy and geometry of the interactions between two isolated (gas phase) molecules are relatively amenable to calculation and hence relatively well understood, the three dimensional, close-packed nature in crystals makes understanding the ways in which they are held together considerably more challenging. Ultimately, computational crystal structure prediction (CSP) methods may well hold the key to a holistic understanding of the full spectrum of intermolecular interactions in crystals. Indeed it is only through a full understanding of the contribution to the overall stability of all of the long and short range contacts made by a given molecule in a crystal that it will be ultimately possible to reliably predict the most stable crystal structure. Even then, nucleation and growth considerations may mean that the most stable structure is not experimentally accessible and hence an understanding of intermolecular interactions at all stages along the crystal formation pathway is really what is required. Such information remains beyond the scope of even the very powerful CSP methods currently available[20] although it is noteworthy that recent Cambridge Blind Tests have produced some remarkable successes.[21] In the case of multi-component systems the CSP challenge is even more daunting because of the additional degrees of freedom and hence possible structures enabled by the presence of a second component[22] and in practical terms the understanding of multi-component crystals is often based on empirical data gathering and rationalisation. However, experience in common association modes coupled with empirical rules[23-25] and carefully targeted calculations can give insight into likely cocrystal and salt formation. A good example is the deliberate engineering of ternary (three-component) cocrystals based on observations of the best hydrogen bond donor/best acceptor pairings.[26] More recently a combined understanding of pK_a values, hydrogen bond basicity (β -values), and supramolecular synthon history has been used to engineer further ternary cocrystal systems as in acridine-3-hydroxybenzoic acid· 2-amino-4,6-dimethylpyrimidine, Figure 3.[27]

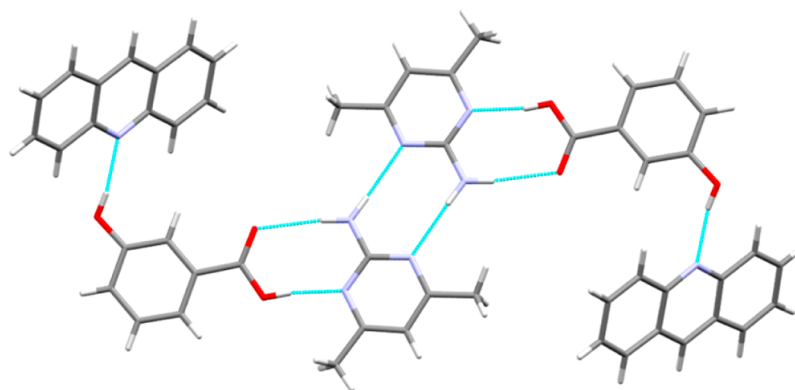


Figure 3. ternary cocrystal of acridine-3-hydroxybenzoic acid- 2-amino-4,6-dimethylpyrimidine prepared by careful balancing of pK_a values, β -values, and supramolecular synthon history (reproduced with permission from reference [27]).

2.3 The Supramolecular Synthon Approach

The supramolecular synthon approach[28] looks for frequently occurring and hence reproducible patterns of intermolecular interactions in order to identify building block type motifs that can be used to design and 'engineer' a crystal or cocrystal structure. Such interactions may be easily recognized like the well-defined carboxylic acid dimer[29] or amide $\text{NH}\cdots\text{O}$ hydrogen bonding motifs, or they may be interactions such as π -stacking, interactions between aliphatic chains or halogen bonding motifs, Figure 4.

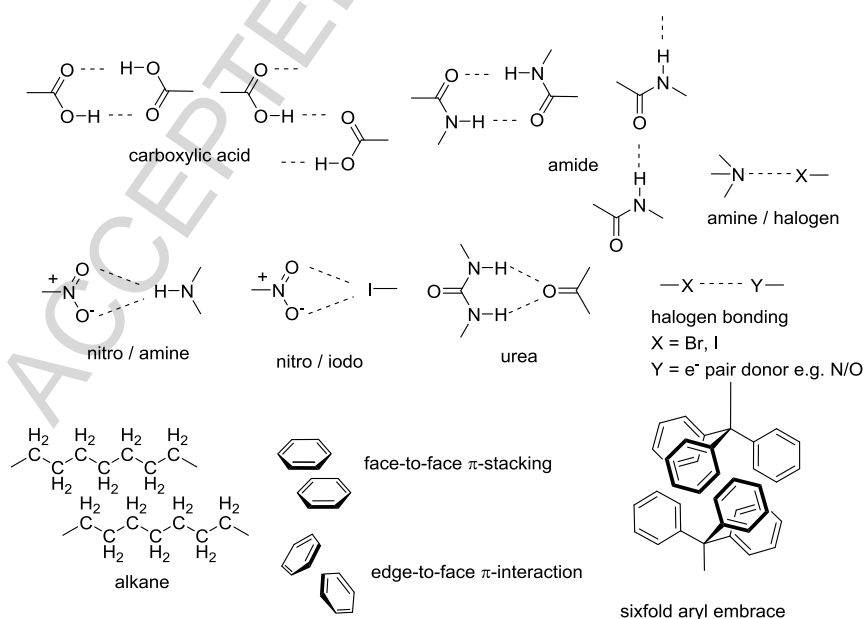


Figure 4. Common supramolecular synthons – interactions between functional groups on different molecules in crystals that can sometimes be used in a predictive fashion to engineer crystal and cocrystal structures.

The supramolecular synthon approach has been used with considerable success in the production of cocrystals, for example the use of the pyridine – carboxylic acid synthon in designing cocrystals of the anti-tuberculosis drug isoniazid, Figure 5.[30] A synthon-based crystal engineering approach has been used to design glutamic acid cocrystals for the poorly soluble sodium channel blocker 2-[4-(4-chloro-2-fluorophenoxy)phenyl]pyrimidine-4-carboxamide, resulting in dramatic solubility enhancement.[31] While the geometry of the pyridine-carboxylic acid synthon is expected to be quite

similar in both neutral and (proton transferred) salt form, in fact the calculated energy of such cocrystals and hence the predicted cocrystal form landscape, is found to be highly sensitive to the proton position.[32] The supramolecular synthon approach is quite useful in predicting the likelihood of cocrystal formation over competing self-sorting of the two components. For example a Cambridge Structural Database[33] analysis showed that the formation of hydroxyl...pyridine supramolecular heterosynthon in crystal structures that contain hydroxyl and pyridine moieties in the absence of other hydrogen-bonding moieties is near-certain, implying that the heterosynthon and others like it such as the hydroxyl...cyano heterosynthon, are strongly favoured over the competing hydroxyl...hydroxyl supramolecular homosynthon, giving rise to a synthon hierarchy.[34]

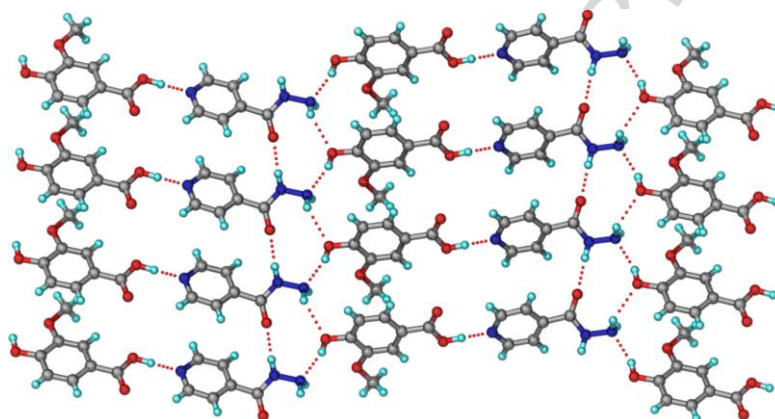


Figure 5. Sheet structure of Form 2 isoniazid-vanillic acid assembled via N-H...O, O-H...N hydrogen bonds, and the acid...pyridine supramolecular heterosynthon (reproduced with permission from ref. [30])

2.4 Ionic interactions - Salt vs. Cocrystal Formation

Transfer of a proton in solution carries little steric consequence because of the proton's small size and hence the protonation of a base by an acid (commonly an amine or nitrogen heterocyclic base by a mineral or carboxylic acid, for example[35]) is governed solely by well understood electronic factors in combination with the solvation properties of the acid, base and the resulting salt. These factors are reflected in the thermodynamic pK_a values of the acid and the conjugate acid of the base and represent their Brønsted acidity. The pK_a represents the pH at which the solubilised population's ionisable group or groups are 50% charged and 50% protonated and is dependent on the acid/base strength of the molecule. Strictly speaking bases should be defined by their pK_b , but this is seldom used in practice. So if a molecule has a pK_a of 11 analysis of the structure to determine whether a weak acid or strong base is being described would be necessary.[1] This concept of salt and cocrystal formation is dealt with in more depth in section 3 where the design of salts and cocrystals in solution is considered. From the pK_a the equilibrium concentration of ions can be calculated and if the pK_a difference between acid and the protonated base is more than 2-3 log units then proton transfer is essentially complete. Similarly, for a given solid state reaction this ΔpK_a rule generally holds true and salt formation is expected,[36] although recent theoretical and high pressure studies have shown that proton transfer in the pyridine-formic acid system is dependent on the amount of formic acid present.[37, 38] Ions are charged and interact strongly with polar molecules, particularly water, and hence salts are often highly hygroscopic, especially when the anion is a conjugate base of a strong acid such as sulfate, hydrogen phosphate or chloride, for example. In terms of intermolecular interactions the situation is fairly easy to rationalise, at least in broad terms. While the salt is often held together by strong charge-assisted hydrogen bonding interactions, such as the $-NH_3^+ \dots OHSO_3^-$ hydrogen bonding in clopidogrel hydrogen sulfate (Figure 6),[39] this single hydrogen bonding interaction frequently leaves much of one or more of the ions with exposed polar functionality. This

exposed region of charge can be stabilised by additional interactions to water, particularly in the case of larger organic cations and anions with a high hydration energy such as sulfate.[40] This is the case with the antibacterial trimethoprim sulfate trihydrate, for example.[41] In extreme cases absorption of water by the ions results in a highly concentrated salt solution which then acquires more water from the atmosphere by osmosis giving rise to the phenomenon of deliquescence. Under these circumstances isolation of a stable crystalline salt under ambient temperature and humidity is often not possible and the material is unsuitable for drug formulation. Similarly, salts frequently form stoichiometric hydrates[42, 43] in which the exposed faces of the component ions are stabilised by the incorporation of crystallographically well defined sites containing water. In the case of metal ions crystalline hydrates can similarly form in which the water coordinates to exposed faces of the metal cation. These species are now more properly termed metal aquo complexes. In the era before their structural chemistry was well understood,[44] their identification by water content and elemental composition alone meant the metal ion coordination and crystal lattice incorporation by hydrogen bonding were not possible to distinguish. In fact, simple empirical formulae can mask extremely complex structural chemistry as in the mixed hydrate / butanol solvate of the magnesium salt of esomeprazole, which contains both a magnesium hexaquo ion, magnesium tris(esomeprazole-H) anions containing deprotonated esomeprazole as bidentate ligands and molecules of both water and butanol hydrogen bonded within the crystal lattice. The overall formula is thus $[\text{Mg}(\text{H}_2\text{O})_6][\text{Mg}(\text{esomeprazolate})_3]_2 \cdot 6\text{H}_2\text{O} \cdot 6\text{BuOH}$ rather than the simplified “ $\text{Mg}(\text{esomeprazole})_2 \cdot 4\text{H}_2\text{O} \cdot 2\text{BuOH}$ ” and all of the components are linked in an extensive hydrogen bonded network, Figure 7.[45] The patent literature suggests that the structure of a number of commercially important magnesium esomeprazole salts may be similar.[46] Note that just like salts, cocrystals can also form hydrates as in a four-component neutral cocrystal of the antitumor prodrug temozolomide, namely tris(temozolomide) 3-phenylacrylic acid 4-amino-1H-imidazole-5-carboxamide monohydrate,[47] however the neutral nature of the API and coformer residues makes cocrystal hydrate formation to give what is, effectively , a ternary cocrystal, rather less common.

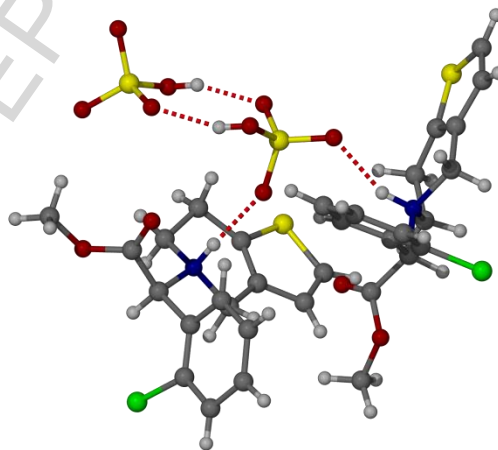


Figure 6. Charge assisted $\text{NH}^+ \cdots \text{O}^-$ hydrogen bonding in clopidogrel hydrogensulfate.[39]

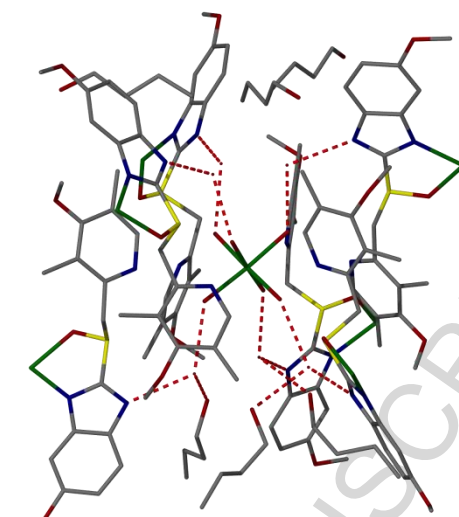


Figure 7. The complex structure of the mixed aquo complex – crystalline hydrate $[\text{Mg}(\text{H}_2\text{O})_6][\text{Mg}(\text{esomeprazolate})_3]_2 \cdot 6\text{H}_2\text{O} \cdot 6\text{BuOH}$. [45] Only the crystallographically unique portion of the $[\text{Mg}(\text{esomeprazolate})_3]^-$ ions is shown (one third of the ion).

If there is a pK_a difference of less than two units between acidic and basic components then proton transfer from acid to base becomes less certain. It is a weakness of chemical nomenclature that the difference between a cocrystal and a salt in an acid-base system can come down to the precise location of a hydrogen ion. If it is close to the base then the system is a salt; if it remains close to the parent acid (even while strongly hydrogen bonded to the base component) it is a cocrystal! The fine differences between salt and cocrystal in these cases has been described by Aakeröy. [48] Indeed in some cases proton position is temperature dependent and simple warming can, semantically, transform a salt into a cocrystal. In some cases such as the urea-phosphoric acid cocrystal (or uronium dihydrogen phosphate salt) there exists a window in which the situation is ambiguous when the proton is equally shared between the donor and acceptor groups. [49] However, there are clearly cases with low pK_a difference in which proton transfer does not occur and any multi-component crystal is therefore a cocrystal.

Ionic interactions are typically properties of salts, or salt cocrystals. They are strong but non-directional, resulting in close packed ionic solids such as NaCl. Commonly in pharmaceutical salts ionic interactions act in concert with hydrogen bonding or coordination interactions and can involve charge-assisted hydrogen bonding (Figure 6; an interaction sometimes termed a “salt bridge” in protein chemistry) or direct coordination of an anionic residue to a metal cation as in the complex anions in magnesium esomeprazole (Figure 7). Ions may also be solvent separated as in the antioxidant sodium 5'-O-phosphonopyridoxylidenerhodanine hydrate [50] in which the sodium cations are fully hydrated and interact with the anions only via second sphere hydrogen bonding. Ionic bonds can also involve less specific interactions between organic ion pairs lacking an acidic proton as in propantheline cyclamate in which the $-\text{NMe}(\text{iPr})_2^+$ group forms a range of $\text{CH}\cdots\text{O}$ interactions with the cyclohexylsulfamate counter anion (Figure 8). Such weakly interacting salts derived from APIs and GRAS materials have been explored as active ionic liquids. [51]

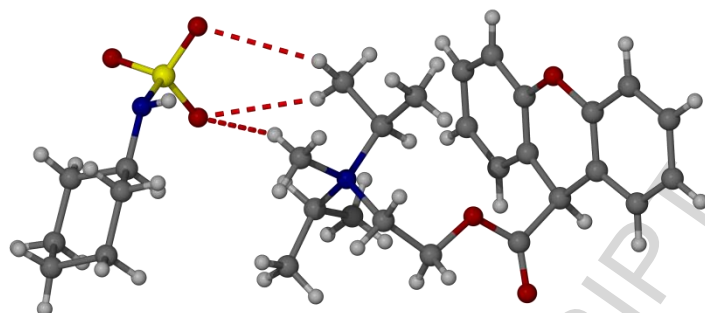


Figure 8. Multiple CH...O interactions in the salt propantheline cyclamate.[51]

2.5 Dipolar interactions

Dipolar interactions in general are relatively weak and, while directional, they are not as obvious or readily applied in cocrystal formation as hydrogen bonding (which is a particular type of dipolar interaction). Dipolar interactions between carbonyl groups, for example, occur in liquids such as acetone and the weaker nature of carbonyl dipolar interactions compared to hydrogen bonds is evident in the low boiling point of acetone (56 °C) compared to water (100 °C). There are relatively few cocrystals in which the components only exhibit dipolar interactions without hydrogen bonding (one example is the acetone solvate of odyendane, a Congolese folk medicine[52]), however dipolar interactions in polymorphs and cocrystals are hugely important in solid state NMR spectroscopic techniques since they give information about intermolecular distances and mutual orientation. This data can result in direct structure determination either by NMR alone or in combination with complementary techniques such as XRPD, giving rise to the emerging area of NMR crystallography.[53]

2.6 Hydrogen bonding

Hydrogen bonding, because of its strength, directionality and ubiquitous occurrence in drug-like molecules is by far the most important interaction in cocrystal design and many cocrystals are formed between weak acids and weak bases (pK_a difference of less than 2 units) and are linked by hydrogen bonding. Hydrogen bonds are strong enough to persist in solution and it is not unreasonable to suspect solution association of API and coformer before crystallization in some cases, as in the carbamazepine- 4-aminobenzoic acid system.[54] In the absence of highly basic moieties salt formation can be extremely challenging and cocrystallization becomes an attractive possibility in searching for more soluble forms of highly insoluble drugs. One of the greatest solubility enhancements seen so far in terms of API/cocrystal maximum *in vivo* concentration (C_{max}) is for the tartaric acid cocrystal of the Phosphodiesterase-IV Inhibitor L-883555. Analysis of the pK_a values of the free base indicate that the most basic nitrogen atom with a pK_a of 4.21 (Figure 9) is too weak a base to be protonated by tartaric acid (pK_{a1} 2.89) and hence a cocrystal is expected. In fact IR and CP-MAS NMR measurements indicated that the tartaric acid exhibits variable incorporation into channels within the API structure and that no proton transfer occurs, resulting in a true cocrystal with hydrogen bonding to the *N*-oxide oxygen atom acceptor.[55]

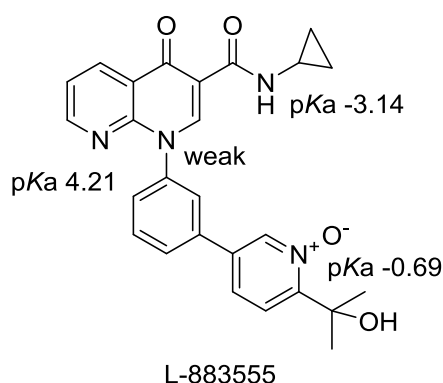


Figure 9. Structure and pK_a values of L-883555.[55]

2.7 π - π Interactions

π -Stacking interactions occur in either an offset face-to-face or edge-to-face geometry in order to maximise the interactions between the electron rich and electron deficient regions of the aromatic ring quadrupoles. These π - π interactions are very important in stabilising many cocrystal systems in which there is an aromatic ring. Cocrystals of aromatic heterocycles such as caffeine and theophylline with benzoic acids are obvious examples, albeit additionally stabilised by hydrogen bonding (Figure 10). As an interesting aside the caffeine-benzoic acid cocrystal was calculated to exist but was only recently prepared with the help of carefully designed heteroseeding.[56] Eclipsed face-to-face π -stacking is unusual but has been observed in cocrystals of electron rich and electron deficient systems. Two of the simplest and most striking are the 1:1 cocrystals of electron rich benzene[57] and bis(benzene) chromium(0)[58] with the electron deficient π -system of hexafluorobenzene. In both systems the aromatic ring planes are directly on top of one another with an interplanar distance of around 3.4 Å, Figure 11.

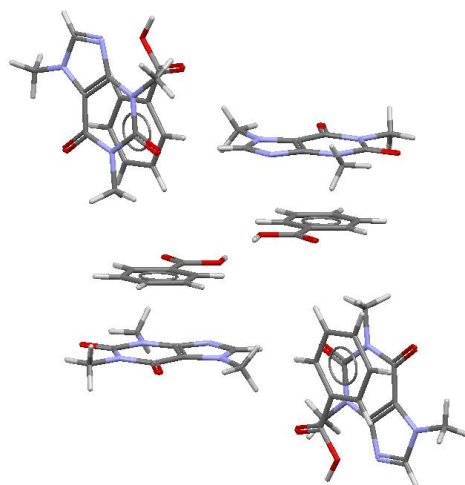


Figure 10. π -stacking in the 1:1 cocrystal of caffeine and benzoic acid.[56]

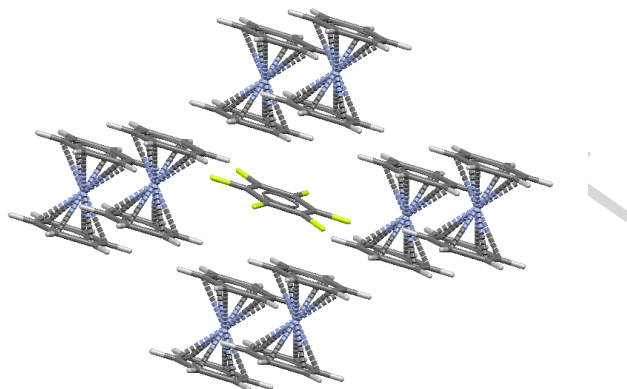


Figure 11. Environment of one molecule of C_6F_6 in its 1:1 cocrystal with bis(benzene)chromium(0).[58]

2.8 Ion- π interactions

The interactions of cations such as K^+ with aromatic rings has long been recognized and is of equivalent strength to a hydrogen bond (around 80 kJ mol^{-1}). [59] More recently anion- π interactions have also come under intense scrutiny. [60] Both are found in salts of aromatic compounds and can exert a stabilising influence. One of the most appealing is Harrowfield's "Calixarene Cupped Caesium: a Coordination Conundrum" [61] in which a single Cs^+ ion sits in the middle of the four aromatic rings of a calix[4]arene anion, with $Cs \cdots$ centroid distances of 3.57 \AA , topped by a single molecule of acetonitrile, Figure 12.

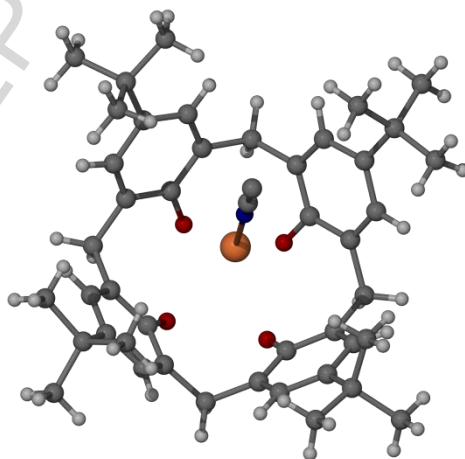


Figure 12. Cation- π interactions stabilise a Cs^+ ion within the hollow of a calix[4]arene anion.[61]

2.9 Halogen Bonding

A halogen bond represents a closed shell interaction between the electron deficient σ -hole opposite a covalently bonded halogen atom, particularly in heavier halogens such as iodine and an electron rich 'halogen bond acceptor' such as a pyridine lone pair. [62] Halogen bonding holds together well-known entities such as polyiodide anions, $I(I_2)_n^-$, and is used medically in wound treatment by povidone-iodine (an iodine complex of polyvinylpyrrolidone). [63] Because of their relatively 'soft' nature,

halogen bonds do not compete particularly strongly with hydrogen bonds, although they often occur simultaneously in structures with both types of chemical functionality. The hydrogen bonded and halogen bonded synthons are often orthogonal and hence offer some degree of predictability in cocrystal design. Halogen bonds have been used to engineer useful cocrystals of 3-iodo-2-propynyl-*N*-butylcarbamate. This material is used globally as a preservative, fungicide, and algicide. It is difficult to purify and handle because of its sticky nature. Cocrystal formation using either alkylammonium iodide to give a salt cocrystal, or bipyridines, results in much more tractable pharmaceutical cocrystals (Figure 13).[64] In another halogen bonded cocrystal system an interesting stepwise mechanism has been identified for the mechanochemical preparation of halogen bonded cocrystals between diiodotetrafluorobenzene and thiomorpholine. The significantly greater strength of the I...N halogen bonded synthon over the I...S interaction results in initial formation of a 2:1 cocrystal comprising only I...N interactions. Prolonged grinding gives a 1:1 phase with both synthons.[65] Halogen bonding between diiodotetrafluorobenzene and iodo-functionalised ureas in combination with pyridyl-ureas has also been used to give two-component halogen bonded gels, potentially useful for pharmaceutical crystallization.[66]

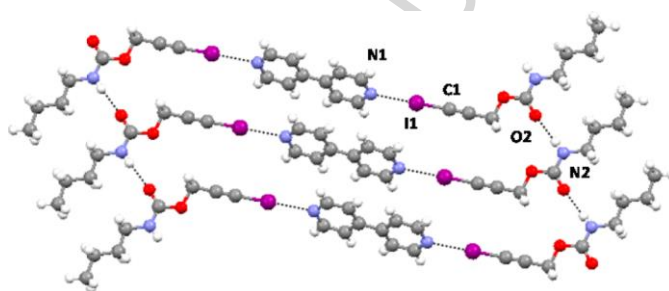


Figure 13. Supramolecular ribbons formed by orthogonal halogen and hydrogen bonding in the 4,4'-bipyridine cocrystal with 3-iodo-2-propynyl-*N*-butylcarbamate.(reproduced with permission from ref. [64])

2.10 Closed Shell Interactions

Along with halogen bonding there exists a range of other closed shell interactions in solids that have some crystal engineering potential, particularly aurophilic[67] and the weaker argentophilic interactions seen in low oxidation state gold and silver complexes. These are manifest in short intermetallic contacts in the solid state structure of these systems and have relativistic origins. A lovely example is the dicyanoaurate salt $[\text{Mn}(1,10\text{-phenanthroline})_2(\text{H}_2\text{O})\{\text{Au}(\text{CN})_2\}][\text{Au}(\text{CN})_2] \cdot 0.5\text{EtOH} \cdot 0.5\text{H}_2\text{O}$ in which an $[\text{Au}(\text{CN})_2]^-$ ligand bound to manganese forms an aurophilic stack with a free dicyanoaurate, Figure 14.

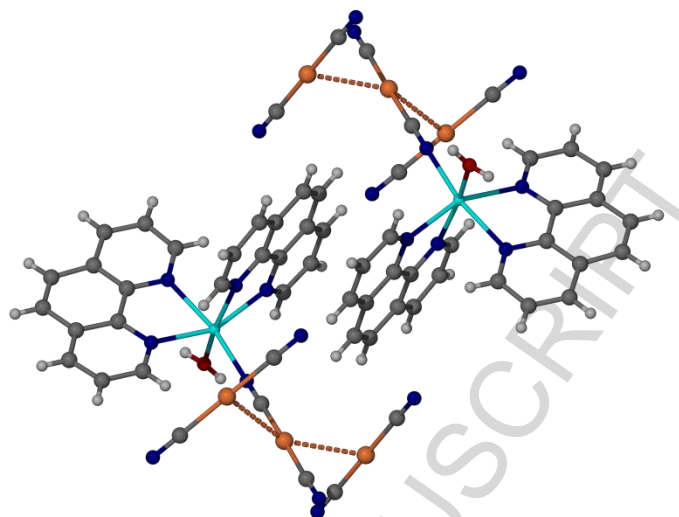


Figure 14. Aurophilic (dotted lines) and π -stacking interactions in the structure of $[\text{Mn}(1,10\text{-phenanthroline})_2(\text{H}_2\text{O})\{\text{Au}(\text{CN})_2\}][\text{Au}(\text{CN})_2]\cdot 0.5\text{EtOH}\cdot 0.5\text{H}_2\text{O}$. [68]

One final class of closed shell interaction is so-called secondary bonding, popularised particularly by Alcock in the 1970's and 1980's. Secondary bonding generally occurs between main group atoms and heteroatoms in crystalline solids and shares some characteristics with hydrogen bonding, leading to some predictability as a supramolecular synthon. [69] An example is Ph_2TeO which contains $\text{Te}\cdots\text{O}$ secondary bonds 2.55 Å long. [70]

2.11 van der Waals Interactions and Molecular Shape

Perhaps one of the most important considerations in cocrystal formation, although one that is difficult to understand and control, is molecular shape. In early clathrate chemistry the tendency of 'awkward' molecular shapes to include solvent or guest molecules and hence form cocrystals was well recognised and led to enduringly effective strategies such as the 'wheel-and-axel' approach to the design of molecules likely to pack poorly and hence form cocrystals. [71] The vast field of calixarene chemistry has evolved from the hard-to-pack molecular bowl shape of the calixarenes and hence their tendency to crystallise with included guests. [72] Molecular crystals are generally characterised by a lack of void space, encompassed in the anthropomorphic Aristotelian adage 'Nature abhors a vacuum'. This close packing arises because van der Waals interactions between molecules are ubiquitous and result in a stabilisation according to the contact surface area. [73] Awkwardly shaped, non-self-complementary molecules are thus highly likely to incorporate other components present in the crystallization medium in order to fill space. This factor is a significant root cause in the incorporation of solvent to give solvates. The ubiquitous presence of water in the atmosphere, its small size and its ability to form hydrogen bonds means that hydrates are the most common solvates. Optimum close packing is sometimes at odds with the formation of strong, directional hydrogen bonding interactions and hence some polymorphic systems arise from a trade-off between optimization of intermolecular interactions and optimization of close packing. This tension is also evident in the formation of crystals with multiple crystallographically independent molecules ($Z' > 1$). [74] A particularly unusual and informative example is the self-included trimesic acid $\frac{5}{6}$ hydrate. This system involves a channel-containing framework comprising layers of trimesic acid and water molecules which includes further crystallographically distinct unsolvated trimesic acid in channels running throughout the hydrogen bonded structure. [75] This 'guest' trimesic acid can be replaced with other guests such as picric acid to give a ternary cocrystal of trimesic acid, picric acid and water. [76]

The distinct host and guest roles explain the $Z' = 12$ structure and the strange $5/6$ stoichiometry in this fully ordered, stoichiometric structure, Figure 15.

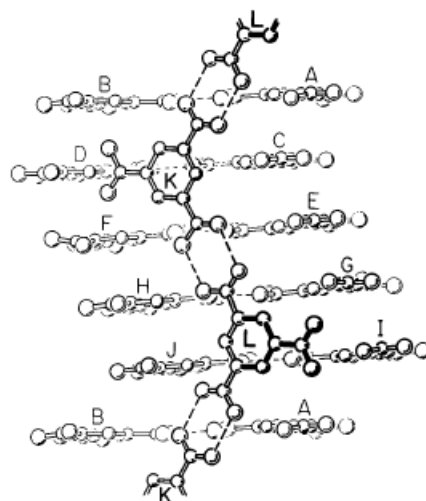


Figure 15. Offset layer packing in $(\text{trimesic acid} \cdot \text{H}_2\text{O})_{10} \cdot (\text{trimesic acid})_2$. Trimesic acid molecules A-J form a channel-containing framework while K and L are the crystallographically independent guests (reproduced with permission from ref. [76]).

3. Molecular level property-based design

Moving forwards from consideration of the intermolecular interactions a number of factors must be considered in order to produce phases that have the optimal pharmaceutical properties. These parameters vary from those which are concerned with the robust reproducible manufacture of the medicine to those directly associated with its absorption *in vivo* (solubility and permeability behaviours). The following section will deal with the molecular level considerations which enable phase design towards these, often competing, end points.

3.1 Screening for binary compositions

It is entirely possible that when two solids are combined that there will be no significant interaction. If, however the solids of two components are brought together as an intimate mixture and there is an interaction, three options are available with respect to their thermodynamic phase behaviours; formation of a conglomerate, formation of a binary phase or formation of a solid solution (Figure 16). Formation of a conglomerate drives the melting point of each component closer to a central minimal value, known as a eutectic, as mole fractions of each component increase. Eutectic compositions have been used in pharmaceutical formulations, most notably the local anaesthetic cream EMLA (Eutectic Mixture of Local Anaesthetics)[77] and it has been proposed that 'failed' cocrystal screens could highlight viable eutectic compositions for further development.[78] Due to their complex characterisation these phases have seldom been developed for oral medicines to date, however. Binary solid compositions in which multiple eutectic points are seen represent the goal of many screening activities. Generally the intention of screening is to generate crystalline salts or cocrystals with defined stoichiometry, phase stability and melting points above 100°C (for appropriate milling) that are readily characterised, as is the hope for polymorphs.[79] The final of the three potential thermodynamic outcomes, for a defined interaction, is a solid solution, where the overall melting point of the solid is determined by the composition. Such phases seldom follow ideality and it is common to represent this by the addition of a dashed line on the phase diagram (such as is seen in Figure 16) as there is commonly variability in the experimentally determined melting point for a given composition.

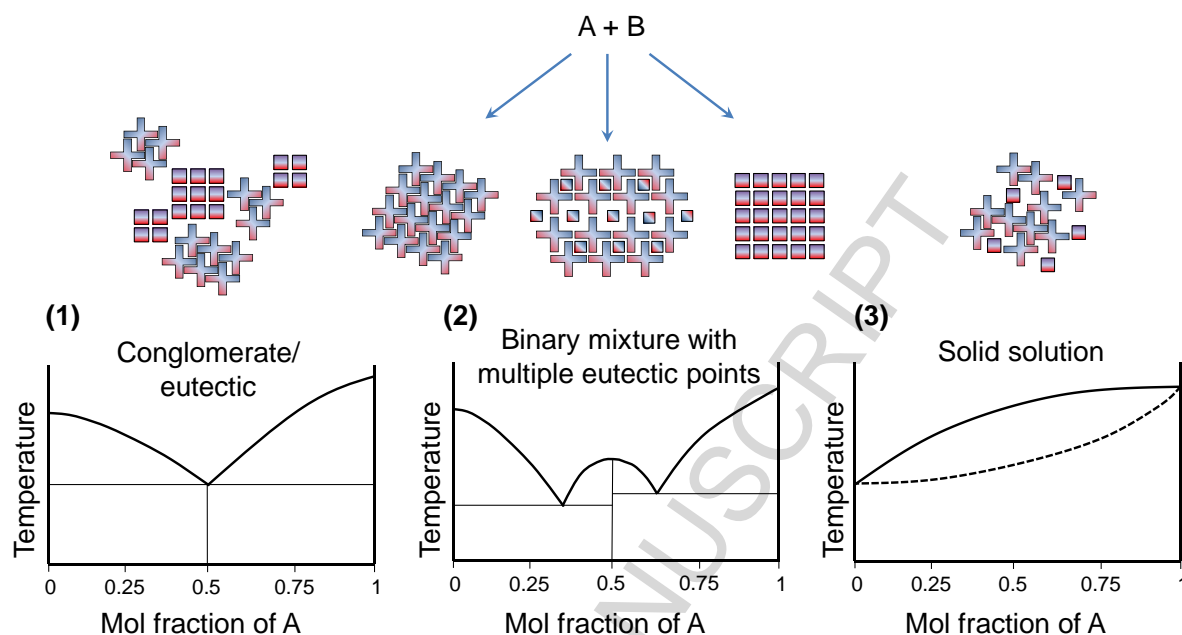


Figure 16. Potential binary behaviours that could be seen in screening for a paired set of interacting solids. (1) Shows a simple eutectic mixture in which the components lead to convergence to a minimal melting point below that of both components. (2) Shows a binary mixture with a new binary phase, in this instance the phase has a lower melting point than the starting components, but intermediate and higher melting points are also possible. (3) Displays the thermal behaviour of a solid solution with the black line depicting the ideal behaviour and the dashed line highlighting potential deviation from ideality.

As discussed in section 2, at the molecular level there are numerous clear differences between salt and cocrystal binding behaviours, but in terms of the binary thermodynamic phase behaviours, salts and cocrystals cannot readily be distinguished if organic counter ions are used; inorganic counter ions have significantly different thermal behaviours and although follow the same rules, do so on different temperature scales. It is the ternary (solution) behaviours that set these phases apart and, for salts, represent the most efficient method for screening for new phases. It is common to screen for cocrystals thermally and through solution behaviours, however. The utility of both DSC[80] and thermal microscopy approaches[81] have been widely discussed. The major problems with screening in this way are thermal decomposition of the API, or the second entity, which can erroneously rule out potentially useful phases and the time cost of thermal microscopy vs. other approaches.

3.2 Solution properties of salts

The details of the physical chemistry of salts have been dealt with elsewhere to an excellent standard,[1, 82, 83] but are included here to highlight key points in salt design. To make a salt an ionisable group in the API molecule, a counter ion for it to interact with and a solubilised population of both components are required, which can interact to form a solid salt. A molecule's aqueous solubility as a function of pH dictates whether a compound will form salts and, if they form, what their properties might be. The charged species of the API and counter ion usually have greater interactions with water and therefore higher solubility. A gap of around 2 pH units, from the pK_a towards charge, is seen to lead to exponentially greater solubility; this can be seen in Figure 16. In practice the continued exponential increase in the size of the charged species' population is stopped by the solubility of the salt, which will be discussed below.

The classic rule of thumb is that a pK_a differential of 3 pH units is required for salt formation between an acid and a base, although a 2 pH unit separation is also often quoted. A study by Brittain has shown the basis of this rule, by studying salts in relation to their equilibrium constant.[84] This rule is based on the solubility enhancement which is seen once both species are charged in solution. A 3 pH unit separation between the pK_a values of the given molecules should maximise the possibility of salt formation and reduce the chance of disproportionation in pure water. This is because at the intermediate pH both molecules have large solubilised populations and therefore opportunity to interact to form a salt. Many examples exist where salts can form with a smaller pK_a separation however[85, 86] and the picture is complicated where multiple ionisable groups are available in a given molecule.[83, 87]

The optimal method for the screening for salts and cocrystals has been the focus of many articles over the last decade.[88-90] Salts have long been screened for by utilisation of the solubility product K_{sp} (Equation 1). This constant is defined by the concentrations of the charged species in solution and is a constant for a given salt (tosylate, maleate etc.) which is based on the salt's equilibrium solubility; not the intrinsic (uncharged) equilibrium solubility of the free API.

$$K_{sp} = [Drug\ ion][Salt\ counterion] \quad (1)$$

K_{sp} is intrinsically linked to the concept of pH_{max} . This is the pH of maximal salt solubility; it is also the pH point which determines the equilibrium solid product obtained from solution. In the case of a base, at pH values below the pH_{max} it is accepted that the resultant solid will be the desired salt, at pH values above it the free base will be the precipitation 'solubility' product of a supersaturated solution. This factor also has significant impact on the likely stability of a salt once it has been produced,[84, 85] so pH_{max} has value in understanding both the production and utility of salts. Figure 17 graphically depicts how a change in the salt can alter the K_{sp} and pH_{max} . Here it can be seen that a change from the tosylate salt (C) to the HCl salt (A) leads to a 95% shift in the K_{sp} value; where the K_{sp} of salt C is 5% of the value of the K_{sp} of salt A. Such shifts have significant implications on the formation and stability of a salt, this is especially pertinent in weak bases which represent many pharmaceutical small molecules.

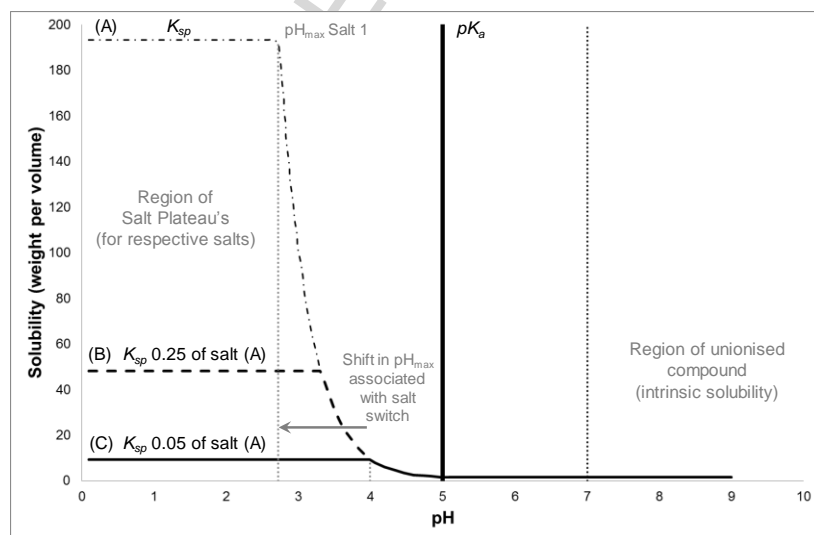


Figure 17. Solubility diagram of salts of a weak base having a low intrinsic solubility and pK_a of 5.0, with salt forms: (a) hydrochloride: pK_a -6.0, (b) sulphate: pK_a -3.0,1.92, and (c) tosylate: pK_a -1.34, having solubility of 200, 50, and 10 (weight per volume), respectively (adapted from reference[85]).

As the K_{sp} is a constant, re-arrangement of equation 1 shows that an excess of counter ion in solution (for a given salt) will drive the formation of the solid of the salt (Equation 2). This has been the underpinning factor for salt screening strategies for some time i.e. an excess of counter ion added to a solution of drug in a solvent.[36] It is also the reason that the common ion effect is seen in HCl salts. In the common ion effect excess HCl present in stomach acid reduces the solubility of the salt, which will affect its utility *in vivo*. [91] This can have a significant effect on the dissolution, and subsequent utility, of HCl salts.[82]

$$[Drug\ ion] = \frac{K_{sp}}{[Salt\ counterion]} \quad (2)$$

Figure 17 also shows a shift in the pH of maximal solubility (pH_{max}) from pH 4 to pH 2.7 when changing from salt C to salt A. This can be determined from Equation 3. It is important to be aware of this, as when in solution above the pH_{max} ($> pH\ 2.8$ in this instance) the free base could precipitate.

$$pH_{max} = pK_a + \log \frac{[B]_s}{\sqrt{K_{sp}}} \quad (3)$$

It should be noted that only at pH_{max} can crystalline solids of both the free base/acid (drug) and the salt co-exist. This means that at this invariant point the solubilities for the free 'species' and the salt are equivalent and is the basis for the ability to derive equation 3 where base concentration ($[B]_s$) is directly related to K_{sp} . [82] $[B]_s$ is also called the intrinsic solubility (S_o) in the literature and is the solubility of the uncharged species. S_o can be experimentally determined (for a base) at pH values well above the pK_a , and remains an invariant amount of a solution population at all pH values because the population of charged species rises with pH shifts. The relationship between the factors in equation 3 has led to derivation of the following outcomes:

- A) An increase in pK_a , of the free base, by one pH unit will lead to an increase in pH_{max} by one unit too. To achieve this practically needs a modification to the drug molecule in question.
- B) An increase in the intrinsic solubility of the base by one order of magnitude increases the pH_{max} by one unit. Again this requires API modification to make it a useful strategy.
- C) A decrease in salt solubility (K_{sp}) by one order of magnitude increases pH_{max} by one unit. This property can be altered by the selection of differing counter ions and if a salt forms would lead to a greater pH range under which it is stable, but at the cost of lower solubility.

The importance of these factors on the design of salts is that if the pK_a of a base is low and/or that the solubility of the API is low then the chances of salt disproportionation are high because the pH range under which the salt is the equilibrium solid species is limited. Conversely more water soluble drugs which have stronger bases are preferable for the development of stable salts. Similar, though inverse, relationships exist for acidic species. This can be seen in Figure 18, which compiles data on marketed (basic) small molecule drugs to 2011, comparing their pK_a against the selected salt counter ion. Although this data does not describe a direct causal relationship, it is apparent that production of stable pharmaceutical salts of API molecules with a pK_a which is less than 5 is difficult (as it happens infrequently) and in such instances ($pK_a < 5$) it would be rational to consider cocrystals as an alternative physical form.

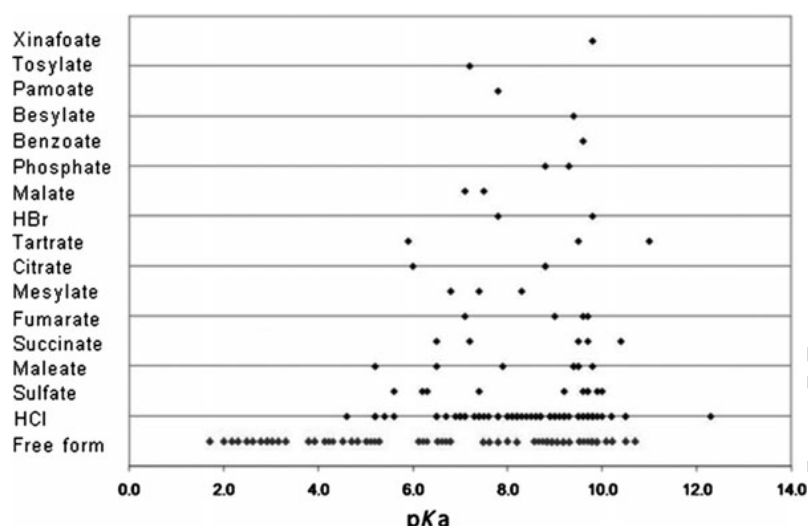


Figure 18. Graph depicting the pK_a of the strongest base within an API versus the free base or salt form chosen for formulation in the product (Reproduced with permission from reference[85]).

Therefore when designing salts, a significant gap (ideally >2 pH units) between the pK_a of the drug molecule and the salt pH_{max} is advisable. This 2 pH unit separation maximises the chance of a high concentration of both species of ions in solution and the best opportunity of salt formation. When considering weak bases, choosing a large pK_a to pH_{max} separation may increase the chances of disproportionation however. This effect is due to reducing the pH range over which the salt is the stable solid product, so a balance should be struck between solubility and stability. Ideally counter ions should also be non-toxic[1] and Stahl[90] organises salt formers into three categories (class I, II and III). These go from ubiquitous counter ions which are commonly found *in vivo* (class I) to those which are not found naturally occurring and are infrequently used (class III). Examples of class I salt forming counter ions would be within hydrochloride and sodium salts. Class II salts tend to involve counter ions that are of vegetable origin and are found in foods, such as malonic acid. Malonic acid is toxic, but half of the lethal oral dose (the LD_{50}) is 4 g in mice[90] i.e. an 8 g dose would be lethal to a mouse, but would represent eating around half its bodyweight (approx. 20 g). Third class salts are those which may be used to solve a particular problem, they are infrequently used and include counter ions such as cyclamic acid, for which there are safety concerns. Finally consideration should also be given to the likelihood of sublimation of the counter ion as in a number of systems this has led to disproportionation of the salt on storage.[92, 93] This same problem is feasible, although as yet unreported, within cocrystal systems.

3.3 Solution properties of uncharged cocrystals

Like salts, the phase behaviour in cocrystal systems has been dealt with elsewhere in a number of high quality papers and reviews.[12, 87, 94-98] There is also a body of excellent work based on the computational screening of cocrystals.[99-107] Discussion of this is beyond the scope of this review, but such approaches have been shown to be effective and improve the efficiency of experimental cocrystal screening.

Cocrystal thermodynamic behaviours differ from salts as they do not require a charged species in order to be able to form, so their solution phase behaviours are commonly represented within isothermal ternary phase diagrams. These represent the three chemical constituents (A + B + solvent) and describe the interplay of phases as the thermodynamically stable result of their mixing at

differing compositions (Figure 19). If a cocrystal exists such diagrams describe a minimum of four phases; the liquid, the crystalline API, the crystalline coformer and the cocrystal. If multiple cocrystals exist the number of phases described within the phase diagram would increase.

The Gibbs rule of phases enables understanding of the construction of the phase diagram:

$$v = c + 2 - \varphi \quad (4)$$

v = variance i.e. the number of variables that can change at a given composition c = number of independent components, this is two in the diagram shown. This is because the cocrystal is a product of the interaction between the API and coformer, meaning they are not independent of each other. So in the diagram shown the independent components are solvent and the solids (API + coformer = cocrystal). The variable φ is the number of phases, which in this example is a maximum of four. It is evident from application of equation (4) that only three phases can exist concurrently at a fixed temperature, however. As the number two in the equation refers to the external parameters of temperature and pressure, this variable is reduced to one in an isothermal diagram. It has been common in the cocrystal literature to date to express thermodynamic data in an isothermal diagram. These diagrams show the thermodynamic product of a given composition and are constructed by application of the phase rule.

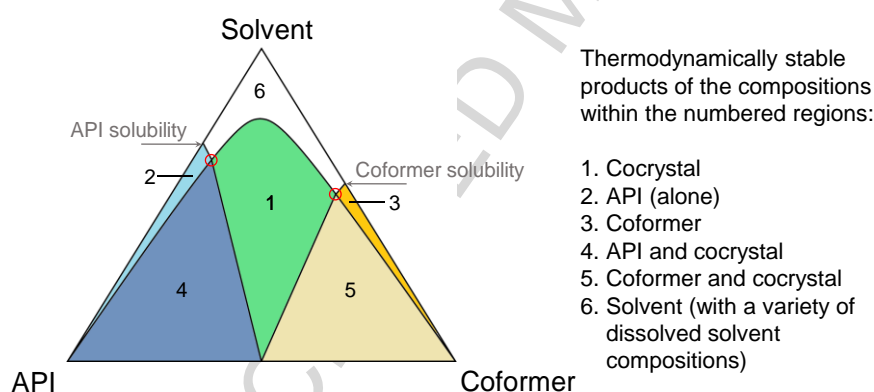


Figure 19. A ternary phase diagram displaying the interplay between API, coformer and solvent. Axes run from 100% (label) to 0% (other component) in mass ratio.

In Figure 19 only zone 6 is able to display significant compositional variance as only one of the independent components is represented (solvent). All other phases are connected as the cocrystal is the product of the interaction between API and coformer, so have fewer degrees of freedom. Zone 6 is therefore able to interact at various compositions with three phases (1= cocrystal, 2= API, and 3 = coformer respectively). Red circles highlight where the composition of the liquid phase is invariant due to application of the phase rule (*i.e.* 3 phases meet). These are also called the eutectic points and represent the compositions where the solid products of the interaction between the components are pure API (right circle as an example) and cocrystal in equilibrium with a fixed liquid composition. These eutectics are comparable to the salt pH_{max} , *i.e.* they are invariant compositions where solids of binary solid and free base can coexist. Eutectic points are normally joined by 'tie lines' to known compositions *i.e.* in a 1:1 cocrystal the 50:50 point between API and coformer and the component in questions 100% composition, as in Figure 19. Within the diagram the remaining unknown compositions in both zones 2 and 3 are between the eutectic (invariant) point and the pure form solubility (API or coformer) *i.e.* the border between zone 2/3 and zone 6. A comparable relationship exists between both eutectic points and the 'central zone' (zone 1) and solvent (zone 6). Within the compositional points that link these three thermodynamic outcomes (*i.e.* the product of zones: 1-6, 2-

6, 3-6), the two phases which are present are solid and solvent. Therefore the compositions at these phase borders are important as they represent the thermodynamic solubility of the mixture in question. The final compositions represented by an isothermal diagram are in zones 4/5. Here three phases are present and pure solid API and cocrystal (as a mixture) are in equilibrium with a fixed composition of liquid (the eutectic point).

Ternary phase diagrams have significant utility in designing crystallisation processes and also form the basis for many screening processes.[108-112] For both screening and crystallisation approaches it is very important to select the appropriate solvent. This is because if one of the components shows no solubility in the solvent, significant skew can be seen in the phase diagrams.[113] Ainouz *et al.* determined a number of phase behaviours as the solubility was reduced (Figure 20). From these behaviours they deduced that with decreasing API solubility the zone in which a cocrystal could be obtained first shrank and then disappeared with a shift from roughly equivalent solubility (1/1.2), to 1/3 and around 1/10 of the solubility, respectively. Figure 20 also displays the fact that where fewer solvent molecules will interact with each API molecule, *i.e.* it is less soluble, the ratio of solvent to API will shift; with more API to each solvent molecule. To circumnavigate these problems they suggested the following: the solubility of the API and coformers should be measured in a set of solvents (although solubility prediction across solvents, if one solubility is known, has subsequently improved to a robust standard.[105, 114]) and the solvent displaying the best solubility for both components should be chosen. The skew in such phase diagrams also gives an insight into why solvent drop grinding may find cocrystal phases which cannot be detected by other means.[9, 113]

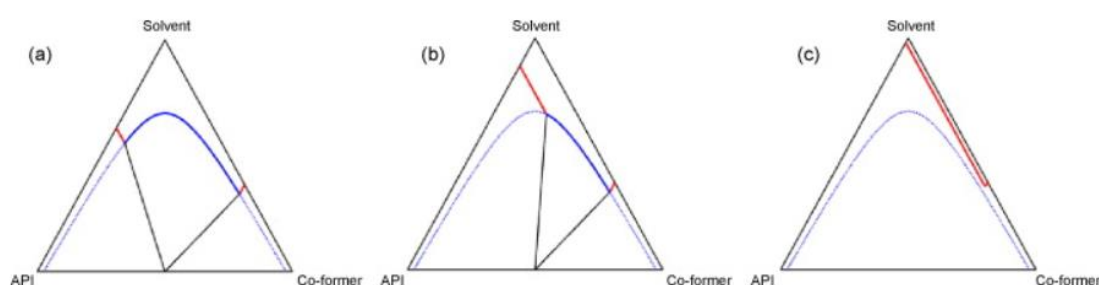


Figure 20. Showing a (a) symmetrical, (b) skewed and then (c) absent cocrystal region as the solubility of the API is reduced from (a)>(b)>(c). Reproduced with permission from reference.[113]

A further key piece of learning that can be derived from investigation of thermodynamic cocrystal relationships is associated with the solubility of the cocrystal phases.[94] Good and Rodríguez-Hornedo investigated the equilibrium of a cocrystal with the solution phase, using chemical potential (μ) to describe this relationship.

$$\mu_{A\alpha B\beta}^{solid} = \alpha(\mu_A^{soln}) + \beta(\mu_B^{soln}) \quad (5)$$

Equation 5 describes the fact that the solubility of the cocrystal (solid AB) is measurable, from a thermodynamic perspective, when solid AB is in equilibrium with A and B in solution. Analysis of the phase diagram shows that at the transition concentration (phase border) the solution is saturated with A (which is API in this example). At this border the chemical potential of the solid drug and drug in solution are equal, because they are at equilibrium.

$$\mu_A^{soln} = \mu_A^{solid} \quad (6)$$

When considering one uncharged drug substance the chemical potential of the solid (μ_A^{solid}) remains constant across phase space and it is possible to substitute the chemical potential of drug in solution

(μ_A^{soln}) for the saturated concentration of the API (C). This means that the relationship of cocrystal solubility can be simplified to the following:

$$\mu_{A\alpha B\beta}^{solid} = \beta(\mu_A^{soln}) + C \quad (7)$$

It is clear from this relationship that the chemical potential of the cocrystal is proportional to that of the coformer *i.e.* a more soluble coformer will lead to a proportionally more soluble cocrystal. Therefore ternary phase diagrams show two key cocrystal behaviours which can be used for effective cocrystal design:

1. A more soluble coformer will lead to a more soluble cocrystal at equilibrium.
2. A highly skewed solubility profile (API to coformer) may lead to disassociation once a solid is placed in a non-equilibrium environment, such as the dosing of a drug *in vivo*.

With respect to using phase diagrams for screening for new cocrystals, another consideration is the way in which to conduct the search. Solvent drop grinding[115-117] and reaction crystallisation[108] stand out as the 'go to' initial methods and have been seen to find more phases than other methods in a number of systems. Other methods, including computational screening, have also been usefully applied to additional learning about the intermolecular interactions and phase behaviour of the system.[118]

3.4 Solution properties of ionic cocrystals

It is possible for an API compound which forms a cocrystal to have some degree of weak ionic character within its structure. It is entirely possible for the coformer to also possess an ionisable group. This leads to additional complexity with respect to cocrystal solubility behaviours, but also enables the potential to tailor cocrystal release to different regions of the GI tract based on charge, as acidic cofomers will be more soluble in the more basic environment of the small intestine (~pH 6.5). A theoretical study by Bethune *et al.* [87] showed the pH solubility dependence of an acidic coformer against an API with no ionisable group (Figure 21). As the API has no ionisable group its concentration remains constant across the pH range, whereas the coformer's changes. In the Figure the constant API concentration (yellow plane) is intersected by the variable (pH dependent solubility) transition concentration of the coformer. This shows that at increased pH the coformer solubility (displayed by the blue surface) rises. Akin to the common ion effect, increased concentration of the coformer will drive down the cocrystal solubility and cause precipitation of the cocrystal as the solubility product (the thermodynamically stable product at a given composition). Further work in this area has increased the prediction landscape to include temperature as well as pH behaviour.[119-121] This work has also provided additional evidence that changes in pH can affect the solution stability of cocrystals, with the lone parent phases of weakly acid API molecules being the product of the thermodynamic interaction at low pH and cocrystals at higher pH (nicotinamide/succinic acid system) *i.e.* when used orally, in the acidic stomach an 'acidic' cocrystal will disassociate like a weak salt.

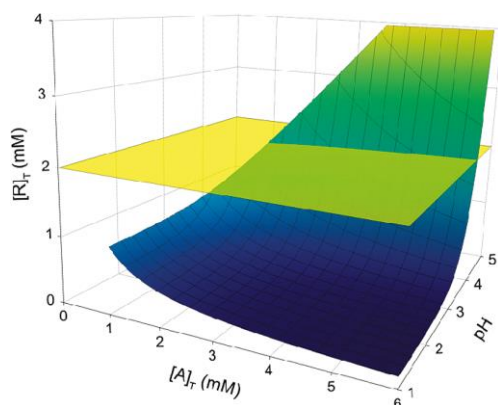


Figure 21. Displaying the theoretical interplay between API concentration $[R]_t$, coformer concentration $[A]_t$ and pH for a non-ionic API and a monoprotic acid coformer (reproduced with permission from reference[87]).

This work has been expanded by the addition of consideration of the solubilisation of surfactants within biorelevant media such as Fasted State Simulated Intestinal Fluid (Fassif) and Fed state Simulated Intestinal Fluid (Fessif).[95] This work concluded that not all cocrystals that have shown a solubility improvement in pure water have a solubility that is higher than that of the parent API in ‘solubilising’ media. Equation 8 displays the link between ‘solubilised’ and ‘pure’ aqueous solubility behaviour that this work determined.

$$SR_{cocrystal} = \sqrt{SR_{drug}} \quad (8)$$

Here the solubility ratio (SR) is defined as the total solubility (ST) in surfactant media (all charged and uncharged species of drug, coformer and surfactant) divided by the aqueous solubility of the cocrystal or parent API at a given pH.

$$\left(\frac{S_T}{S_{aq}}\right)_{cocrystal} = \sqrt{\left(\frac{S_T}{S_{aq}}\right)_{drug}} \quad (9)$$

Due to the common driver for cocrystal selection being solubility enhancement of the API, the drug molecule is often more lipophilic than the hydrophilic coformer and is surfactant solubilised to a greater extent.

The implications of these behaviours, like with weak salts, are that within formulations pH should be monitored. This is because pH changes within the formulation may lead to disassociation of the cocrystal to the starting components. In testing conducted to predict *in vivo* cocrystal behaviour pH speciation should also be considered, as it may lead to a decreased solubility. Solubility in biorelevant media should also always be considered as a more water soluble cocrystal may not carry an *in vivo* advantage. These are thermodynamic behaviours, however. Where disassociation of a cocrystal is predicted it may be possible, through a kinetically stabilised phase, to maintain the benefits through the ‘spring and parachute effect’ (discussed in section 3.6). Given the choice, however, it is less risky to target optimal performance improvements from a thermodynamic perspective.

3.5 Implications of second component choice on physical properties

Appropriate screening methods for cocrystals were the focus of much of the early work within the cocrystal literature. Due to the uncertainty in optimal screening parameters that the work addressed,

it is unsurprising that little attention was paid to consideration of the final use of the resultant phases. Within the broader literature there have now been major advances in the use of individual cocrystals, however. These will be discussed in the following sections.

3.5.1 Melting point

The melting point of a phase is an invaluable tool in determining its physical stability with respect to a given manufacturing route as many processes, such as milling and roller compaction (unless temperature regulated) will lead to an increase in the temperature experienced by the API. Other routes such as hot melt extrusion specifically require the mixture to melt in order for appropriate processing to occur.[10, 122, 123]

It is common for the interaction between coformer and API to lead to a cocrystal of intermediate melting point. In some cases, however, a cocrystal may have a higher or lower melting point than that either of the pure components. Schultheiss and Newman reviewed this behaviour thoroughly in 2009 and determined that 51% of cocrystals possess a melting point between those of the starting components, 39% were lower than either component, 6% were higher and 4% (2/50) were the same. [12] This analysis did not take stoichiometry and hydration into account and was also undertaken on a small dataset, but it is clear that melting point can be manipulated *via* cocrystallisation. For example, the melting point of AMG 517[124] was tailored to some degree by use of cocrystals (Figure 22). It is therefore viable to tune the melting point of a cocrystal to a required process, if appropriate cocrystal phases can be prepared for a given API.

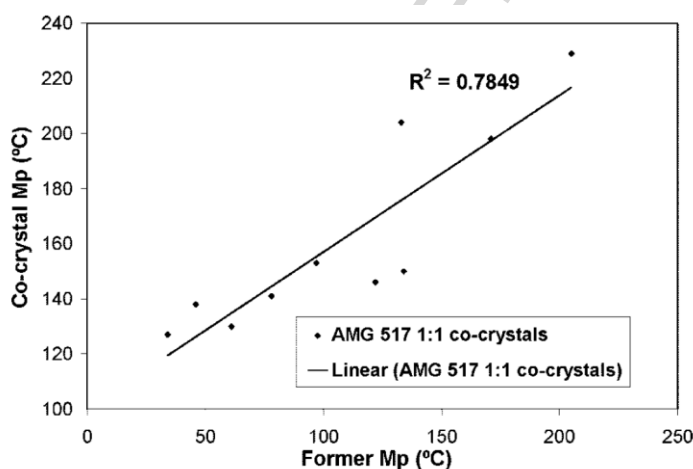


Figure 22. AMG 517 1:1 cocrystals and their melting points vs. coformer, displaying a degree of melting point tuning. With permission from reference.[124]

3.5.2 Hygroscopicity

When materials are stored their behaviour with respect to moisture can have significant impact on their utility and long term stability,[93] both from a chemical and physical stability standpoint. As discussed in section 2 salts can display poor resistance to hydration, cocrystals present a difference here. Indeed one of the first purported benefits of cocrystals, was seen in a system where the resistance of caffeine to hydration was improved.[5] Other cocrystals have also been seen to reduce hygroscopicity when compared to the parent phases alone or in physical mixtures.[13] Resistance to hydration is a consistent behaviour in which cocrystals show a significant advantage over salts, but

not always the parent API.[125] It has also been shown that coformers can lead to deliquescence and subsequent cocrystal formation,[126, 127] so the composition of a formulation should be considered if the excipients used are hygroscopic and have the potential to form cocrystals. Hydration to alternative, less soluble, crystalline states has been shown in the isoniazid-4-hydroxybenzoic acid system,[30] so hydration behaviour should always be monitored throughout development.

3.5.3 Compression behaviours

Poor compression is a problem in pharmaceuticals as both roller compaction, to form granules (which in turn improve powder flow and mixing), as well as tableting require the compression and compaction of materials into a more dense state. In this context compressibility is the potential of a powder to decrease in volume when under pressure, whereas compactibility describes the ability to be compressed into a tablet with a reproducible, and desired, tensile strength. Understanding of the synergistic effects of the material properties of the drug and excipients is essential for appropriate design of a formulation.[128-131] It is entirely possible to formulate around poor compression behaviour by use of excipients to 'drown out' the API properties. Where high dose or high drug loading is needed, within a dosage unit, the compression and compaction behaviour of the API becomes more important. Cocrystal compression behaviours have not been extensively studied to date, but a number of examples exist in which cocrystal phases have shown improvements in tableting performance. [13, 132, 133] Comparison of two carbamazepine systems has been undertaken.[134, 135] In both the carbamazepine-nicotinamide and carbamazepine-saccharin systems an increase in tensile strength for a given pressure was seen with a proportional increase at 1500 lb/cm³ of 2.00 and 2.19 times, respectively. These cocrystals were also seen to have a lower intrinsic dissolution rate than the compacts of the API molecules, an observation attributed to the inverse relationship between higher tensile strength and lower dissolution rate. In other work, analysis of slip planes within the cocrystal structures has been completed to determine their mechanical effect.[136-139] Notable in analysis of these systems are the structural analogues of vanillin in combination with 6-chloro-2,4-dinitro aniline. Here it was seen that slip planes in the ethylene diamine cocrystal led to higher elasticity. The most extreme example of elastic cocrystal behaviour was seen in the caffeine-4-chloro-3-nitrobenzoic acid methanol solvate.[140] Single crystals of this material can recover elastically from deformation into a near complete loop, as displayed in Figure 23. The desolvated structure displayed no such behaviour, although structural collapse was not seen on the loss of solvent,[141] and the elasticity was attributed to the weak dispersive interactions in all three lattice directions. In general it would appear to be prudent to explore slip planes and weak interactions within molecular crystals to modify compression behaviour and the ability to predict such behaviour would be advantageous.

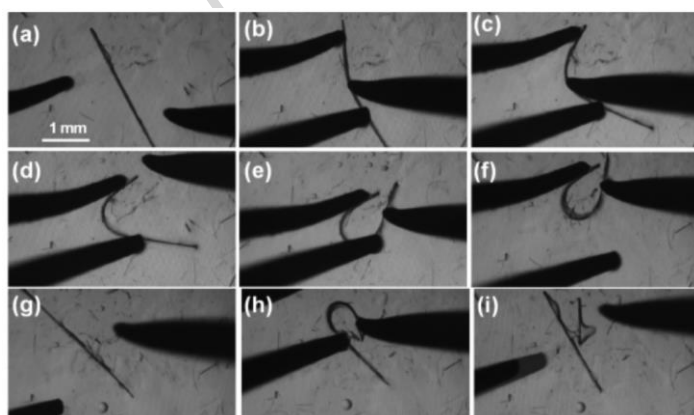


Figure 23. (a) to (g) initial compression and return to initial crystal structure in single crystals of the caffeine : 4-chloro-3-nitrobenzoic acid methanol solvate. (h) to (i) compression beyond breaking point.

3.5.4 Coamorphous materials

The amorphous state is useful in pharmaceuticals as it represents a mechanism by which the solubility can be improved without the need for alterations to be made to the API molecule.[142] The main caveat to amorphous solubilisation is the lack of physical stability that it brings. This is often overcome by use of polymeric materials with high glass transition temperatures to reduce the likelihood of crystallisation.[143-145] This comes at a cost with respect to drug loading though, i.e. each capsule can only contain a small amount of drug because of the large amount of stabilising polymer required. As a result molecular level amorphous dispersion of an API using small molecule coformers offers a distinct advantage. Both coamorphous materials and amorphous salts[146-148] have been seen to be useful in stabilising API molecules and improving their solubility, with an excellent review of coamorphous materials published recently.[149] Neither phase has yet received the degree of research effort seen by stabilisation with polymers and this may in part be due to the inherently comparable glass transition temperatures (T_g 's) within small organic molecules, as compared to the high T_g 's seen in polymers. Application of the Gordon-Taylor equation,[150] displays the negative effect of this behaviour.

$$T_{g12} = \frac{w_1 T_{g1} + K w_2 T_{g2}}{w_1 K w_2} \quad (10)$$

Here T_{g12} is the glass transition of the amorphous mixture and T_{g1} and T_{g2} are the glass transition temperatures within the individual components, w_1 and w_2 are the weight fractions of the components present and K is a constant. Therefore if a polymer with a high T_g is used then the T_g of a mixture will approach this high T_g value as weight fraction increases, as the constant (K) is usually positive. It follows that the fact that small molecules have generally comparable glass transition temperatures may be halting scientific progress in this area. Despite the lack of T_g modification (and subsequent anti-plasticisation) significant increases in stability, and decreases in molecular mobility, have been seen in these phases through increased molecular level interactions.[151-153] Indeed the potential to predict these interactions has been explored using computational pairwise affinity calculations.[154] Amorphous salts cannot always be readily be defined by the Gordon Taylor relationship, as it is impractical to measure the T_g of inorganic counter ions. A study with amorphous indomethacin by Tong et al. showed the change in T_g could be mapped against ionic radius of the counter ion.[147] In this study cation charge was mapped against T_g in a series of monovalent salts. Increases in ionic radius led to an inverse dependence in T_g , shifting from the highest T_g in the lithium salt to the lowest in the caesium salt 139 °C to 69 °C, $\text{Li}^+ > \text{Na}^+ > \text{K}^+ > \text{Rb}^+ > \text{Cs}^+$. Since the strongest electrostatic interaction led to the highest T_g , it was proposed that the sodium salt should be selected, as lithium salts are toxic. Evidence to date would suggest the stability of coamorphous phases is highly moisture content dependent,[149, 154, 155] and that this is also a problem with respect to amorphous salts. None the less, these phases are under studied and represent significant potential for advances in small molecule drug delivery if such properties can be controlled by design or formulation.

3.6 Implications of the second component on dissolution and pharmacokinetics

It is evident that manufacturing routes and quality attributes can be altered by salt formation and the application of cocrystals. Salt forms have been known to modify the bioavailability of API molecules for many years[1] and their behaviours in this respect are well characterised and understood, so will not be dealt with here. Cocrystals are less well known from this perspective and have a growing evidence base in this regard. As such section 3.6 will deal predominantly with the biopharmaceutical implications of cocrystals.

3.6.1. Impact on dissolution

The improvements in *in vitro* dissolution have been shown in many studies and reviews over the last decade for both salts of poorly soluble drug products and cocrystals.[1, 11, 31, 156, 157] Dissolution is a method commonly used to determine a relationship between *in vitro* study and *in vivo* usefulness of a drug product with the rate, extent and profile of the dissolution process being indicative of the biopharmaceutical utility of a given phase.[158] It also represents a key link between kinetic and thermodynamic behaviour, as in some instances short term benefits (a 'spring') can be enough to drive improved *in vivo* absorption. Sometimes the duration of this spring effect is not sufficient however and it is pertinent to seek a nucleation inhibitor or metastable phase which elongates this transient concentration increase, often termed a 'parachute'. A number of the potential dissolution outcomes, such as these, have been seen throughout extensive study and are displayed in Figure 24. It should be noted that although not displayed in the Figure, one potential option is that the new phase has a lower solubility and slower dissolution rate than the parent API, this has been shown in a number of studies.[12] Such a delay in dissolution, although not generally the driver for the study of new phases of pharmaceutical products, could be used to modify the release of products of highly soluble agents and has a great utility in agrochemicals.[159]

Increased solubility phase maintained for the length of the experiment through modification of pH (salts and cocrystals) or other change in the solution environment e.g. hydrotrope assembly created

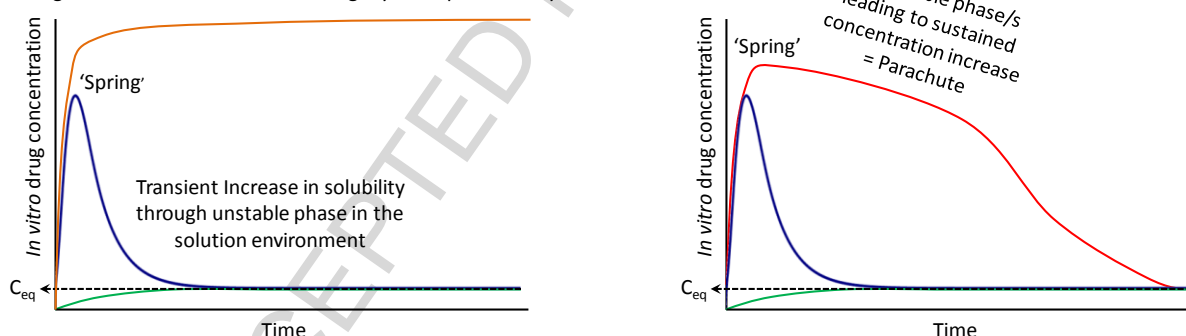


Figure 24. Depiction of the spring and parachute concept to improve dissolution in poorly soluble drugs. The (low solubility) stable polymorph of the free form depicted in green, a spring with no parachute, short lived metastable species, depicted in blue, a sustained solution phase depicted in orange (left) and the spring and parachute model, depicted in red (right). Adapted from reference [157].

It is clear from Figure 24 that there are a number of potential options for the dissolution of a cocrystal or salt and that they can be compared to select the most appropriate phase for *in vivo* utility. Indeed a comparison of the dissolution data for norfloxacin (a compound which has polymorphs,[160] amorphous forms[161], salts and cocrystals[162]) shows the relative benefits of each phase from a biopharmaceutical perspective. This should be considered in the context of the fact that no solubility data exists for the enantiotropic polymorph of norfloxacin, but previously Hancock and Parks showed the solubility difference between polymorphs to be within the region of a maximum of 3 times[142] and subsequent study gave further evidence for this.[163] Within norfloxacin it can be seen that the advantage of the salt over the uncharged cocrystal is significant (46 times better), but the amorphous phase comparable (although undoubtedly superior). A similar circumstance was seen by Almeida and co-workers when looking at the relative supersaturation ratios of a number of phases of CRH1, a model weak base.[164] Here it was seen that the cocrystal was again comparable to the unformulated amorphous phase, but significant improvements in supersaturation were seen when the amorphous

form was formulated, but gave further evidence for a maximal value in supersaturation associated with formulations.[165] It is within the body where sink conditions, generated by drug absorption, enable these differences to be most effectively studied however.

Table 1. Comparative dissolution data for norfloxacin cocrystal, salts and amorphous dispersions

Phase	Solubility ratio
Free base	1.00
Isonicotinamide cocrystal	2.76
Succinic acid salt	31.42
Malonic acid salt	18.57
Maleic acid salt	46.66
Norfloxacin/PVP (70% / 30%)	3.05
Norfloxacin/HPC-L (70% / 30%)	3.85
Norfloxacin/Carbopol (75% /25%)	2.615385
Norfloxacin/PVP/HPC-L (75% /12.5% /12.5%)	5.307692
Norfloxacin/PVP/Carbopol (75%/12.5% /12.5%)	2.87
Norfloxacin/HPC-L/Carbopol (75% /12.5% /12.5%)	3.23

3.7 Basic Pharmacokinetic parameters

The study of pharmacokinetics (PK) defines how much of an API is in the defined 'body' at a certain time. To an extent, study of pharmacokinetics is not a useful endeavour without some knowledge of the pharmacodynamics (PD) of the given drug. The distinction between these two areas is that pharmacodynamics is the study of what the drug does to the body and pharmacokinetics is what the body does to the drug. Pharmacodynamics describes the drug's effect at a given concentration, both desired and toxic, and PK describes its absorption, distribution, metabolism and elimination (ADME). The study of pharmacokinetics, when combined with pharmacodynamic information, enables knowledge of the doses required to yield safe and effective use of a drug. Although there is commonly a relationship between dose and response it does not necessarily hold that drug action will be concentration dependent as this depends on the pharmacology of the agent under study.

At its simplest PK is studied through the single compartment model,[166] although very significant work has been undertaken, for many years, looking at the compartmental distribution of drugs, both empirically and computationally.[167, 168] The single compartment model is where the body is considered to be one compartment with drug only going in and coming out of this 'body'; rather than the true biological complexity that this represents. In this, and other models, it is common to take samples of blood at fixed times to define the ADME process. Blood, and plasma taken from the body, are used as they perfuse other tissues and quickly become homogenous with respect to API concentration, therefore can be representative of the body as a single compartment. Once a suitably robust assay has been defined it is then possible to determine a concentration vs. time relationship for a given drug and, in the context of this review, compare different phases and formulations. An example PK profile showing the key PK parameters can be seen in Figure 25.

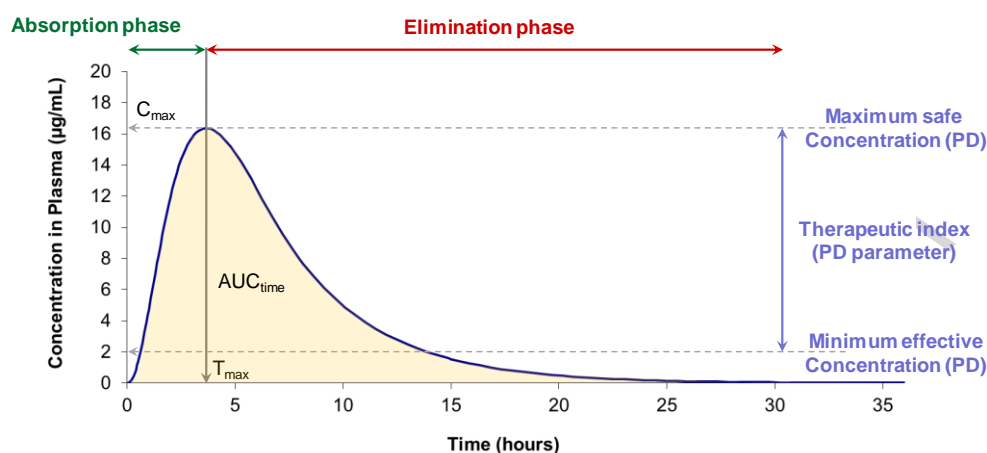


Figure 25. A representative oral PK profile showing C_{max} , T_{max} and AUC (shown in yellow). Half-lives for absorption and clearance processes can be calculated by study of the absorption and elimination phases (green and red respectively).

Absorption and elimination phases represent the period of time in which a given process is dominant. Both processes can be described by their rate and are usually defined by first order processes enabling calculation of a half-life ($t_{1/2}$). It is more common for a reported $t_{1/2}$ to describe clearance, however. It should be noted that absorption processes will still occur into the elimination phase, but will no longer dominate. The time point at which these processes switch dominance is described by the T_{max} . This also describes the time at which the concentration is at its highest within a given study. This parameter can also be usefully applied to calculate the exact C_{max} if it is not seen in sampling. The C_{max} parameter describes the maximum concentration observed in the respective compartment (blood in this example) in a given study. This is an essential parameter as it can be combined with pharmacodynamic information to determine whether a given dose will be effective or toxic. The area under the curve in a time (AUC_{time}) describes the total amount of drug which has been absorbed into the studied compartment over a period of time, and can also be called 'exposure'. The time period associated with the AUC is usually considered to be either for the time of study (e.g. AUC_{0-12} hours) or to infinity ($AUC_{0-\infty}$). It is important that the time frame is defined to enable objective comparison of AUC between studies, as this is used to define differences between an IV dose or alternative formulations. When AUC's are compared, the resultant parameter is presented as a ratio and is the bioavailability, usually denoted as F . It should be noted that when preparing studies for PK to compare bioavailability, appropriate definition of the formulation which was dosed, to the animal species in question, is also essential. Few studies into cocrystal PK to date show content uniformity and stability information for the formulation and this brings the validity of the evidence base into question. For example very few studies using suspension based formulation have overtly presented X-ray data to compare the form of the drug substance with that in the formulation, despite significant evidence of the potential for cocrystal disassociation in solution. It is important that future studies address this deficiency, especially when viewed in the light of cocrystal solution physical stability.[12]

3.8 Impact of cocrystal parameters on *in vivo* PK

Spanning the academic and patent literature there are now a number of studies that display *in vivo* data for the use of cocrystals.[31, 55, 125, 169-191] The dataset is currently small and totals in the region of 74 studies at the time of writing (a study in this context comprises a cocrystal dosed to at least one animal to determine pharmacokinetic parameters of that crystalline phase). This encompasses studies where the number of animals used is between 1 and 6, with the species varying across studies, but remaining constant within a given study. It should be noted that the most

commonly used genus was *Canis* (beagle dog), but *Rattus* species (Wister and Sprague Dawley rats) have also been frequently used. In analysis of these data, studies with multiple doses of the same cocrystal or where formulation modifications have been explored were not considered as multiple studies. As it is difficult to present a dose adjusted comparison of such data, one data point was taken from each of these studies with this consistently associated with the highest delivered dose, i.e. if there were multiple doses the C_{max} from the highest dose was used. This was done to remove the possible effect of formulation additives leading to incomparable clearance parameters, as will be discussed later. This was necessary as it is clear from the available data that coformer choice can affect drug clearance. In some cases information from the PK profile was captured from published PK profiles using a web based XY plotting tool.[192] Such tools are invaluable in the determination of published pharmacokinetic data where parameters are not always described coherently across multiple datasets e.g. AUC values are presented but not tabulated C_{max} information. Some datasets were not complete with respect to solubility information (cocrystal vs. parent), where this was the case comparison of the ratio of intrinsic dissolution rate (cocrystal vs. parent) was used. Intrinsic dissolution rate has previously been described to be a superior measure for *in vivo* prediction in the early development environment.[83] If this was also not available the linear portion (initial time points) of the dissolution rate was used as an indicator of solubility ratio (parent API/cocrystal). Where neither solubility nor dissolution data were present, for a given phase, the point was omitted from the plot. Data for the relationship between cocrystal solubility and C_{max} can be seen in Figure 26.

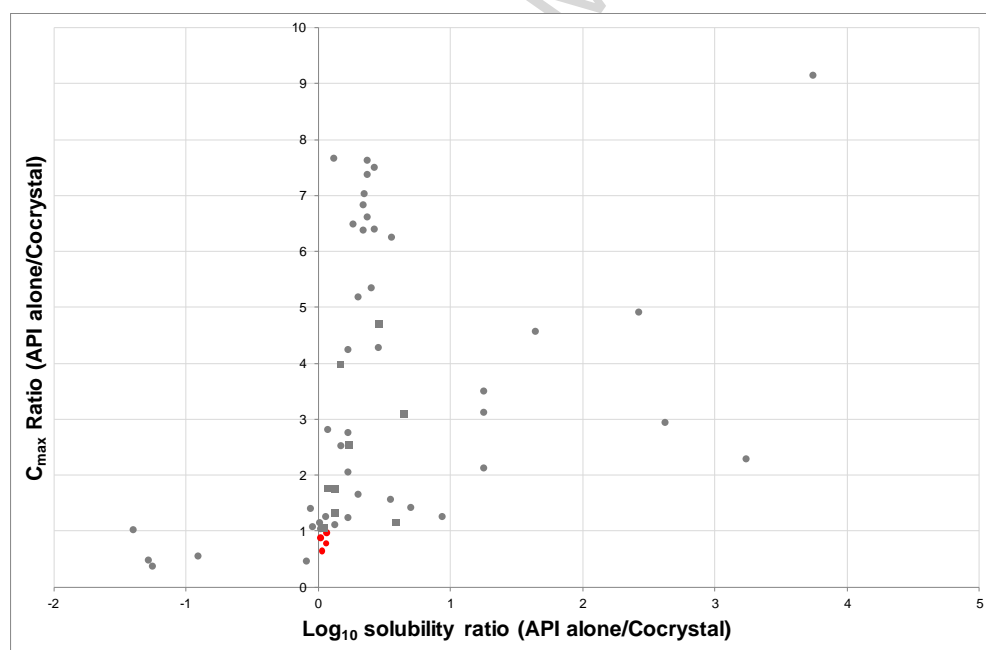


Figure 26. Correlation between Log_{10} *in vitro* solubility ratio (API/cocrystal) and *in vivo* C_{max} ratio (API/cocrystal). Square data markers indicate that dissolution data was used instead of directly sourced solubility information. Red markers display points where improved *in vitro* solubility did not translate to *in vivo* improvement.

No clear statistical relationship can be drawn from this plot, indeed the maximum *in vivo* improvement (C_{max} ratio) seen in a cocrystal is not plotted here as no *in vitro* solubility information is available.[175] Here a cilostazol-4-hydroxybenzoic acid cocrystal was seen to have a 14.6 times improvement in C_{max} ratio. Insufficient evidence is available to determine the structural basis of this *in vivo* performance though. The maximum improvement presented in this data is from a quercetin-caffeine-methanol solvate.[188] Here it is evident that the inclusion of the solvent molecule may be aiding the *in vitro* solubility and *in vivo* performance. Sadly the toxicity of methanol would limit

this as a planned strategy for dose delivery. It is evident from Figure 26 that if *in vitro* data show a significant increase in aqueous solubility for a given cocrystal, then an increase in C_{\max} is both possible and likely. Shan *et al.* [175] previously completed a similar analysis of the cocrystal literature in an excellent review on the topic and drew the same conclusion. Within this work the authors also showed that an increase in C_{\max} correlates with an increase in AUC. It should be noted however that four of the studied systems which displayed a marginal increase (< 20% increase) in *in vitro* solubility vs. the parent API did not convey any *in vivo* advantage. These systems were lamotrigine: nicotinamide (1:1), meloxicam: fumaric acid (2:1), meloxicam: glycolic acid (1:1) and paliperidone: 4-aminobenzoic acid (1:1).[171, 173, 191] In the case of lamotrigine it is possible that conversion to the known, less soluble, hydrate phase occurred. In the meloxicam examples the elimination phase of the PK profile was not explored within the 4 hour extent of the study, so it is possible that the true C_{\max} for these examples was not realised as the concentration was still rising at the final time point. The paliperidone example is within error of being the same as the parent API (97% of parent $C_{\max} \pm 11\%$ variance in results). Combining the overall trend seen in these data with the previous knowledge that more soluble coformers tend to increase the solubility of the resultant cocrystal[87, 175] should aid the design of phases which improve bioavailability. It is clear that this logic does not always hold true however and a number of cases show that caution should be applied when designing cocrystals in this fashion.

With this fact in mind and the knowledge that *in vivo* bioavailability has long been known to be a combination of both permeability and solubility, most notably considered in the BCS classification system,[158] it is pertinent to explore permeability effects in cocrystals. Discussion of the implications of API permeability and biorelevant solubility have been addressed by a number of authors,[95, 98] but discussion of the coformers' permeability characteristics have not been a significant feature in the literature. Therefore it is rational to determine if the permeability of coformers has an *in vivo* impact. Further analysis of the published PK data reveals that there is indeed a relationship between Log *P* of the drug and coformer and improvements *in vivo*. This can be seen in Figure 27. Here published Log *P* data (Chempidder[193]) and calculated (Marvin[194]) Log *P* values were used to compare the ratio of Log *P* (coformer/API) to the *in vivo* improvement in bioavailability, as determined by an increase in C_{\max} . This is valid due to the linear relationship between AUC and C_{\max} in cocrystals.[175]

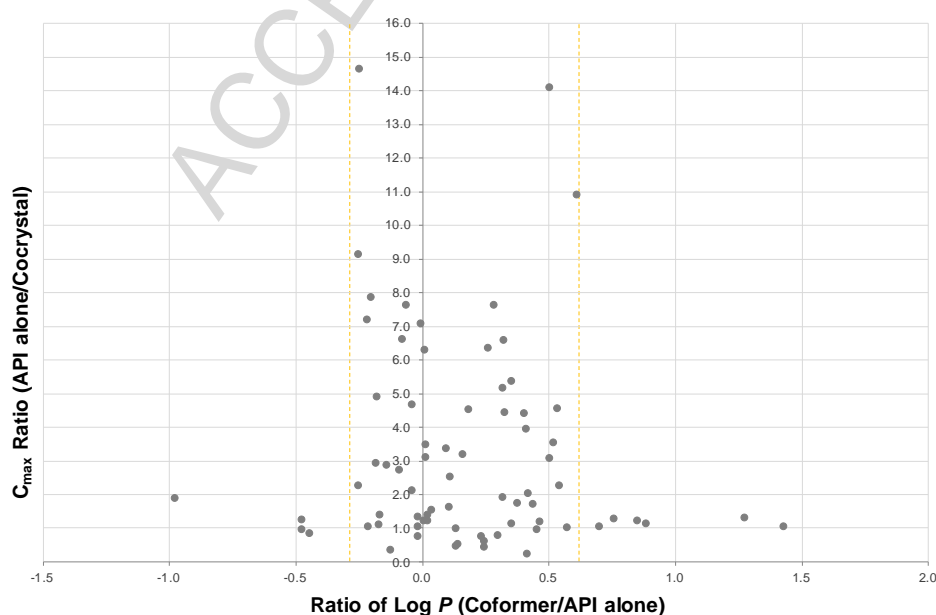


Figure 27. X-Y Scatter plot showing difference in C_{\max} from the parent (1.0 is parent API C_{\max}) vs. the Log *P* ratio of the coformer to API. Significant differences in Log *P* between API:coformer ($>\pm 0.6$ ratio) appear to lead to no C_{\max} improvement from the parent API.

It is evident from this plot that if the rationale for cocrystal production and selection is an improvement in PK (in terms of bioavailability) then this is unlikely to be achieved if the ratio of coformer to API Log P is significantly greater than ± 0.6 (unitless ratio). The lack of improvement when the ratio is large is thought to be due to disassociation of the cocrystal in water if one component is much more water soluble than the other and correlates with data from *in vitro* studies.[95] This observation adds weight to the caveat that increasing the solubility of the coformer will not always improve dissolution i.e. if the Log P difference is large the benefit will not be conveyed to the *in vivo* state. Significant decreases in C_{\max} are not seen in the data points beyond the ± 0.6 cut-off however with the majority of systems showing comparable PK to the parent API. So if a non-PK parameter is the driver for cocrystal selection e.g. hygroscopicity of the free drug, then it may prove prudent to explore cofomers with large log P differences to the parent API.

Sitting within the ± 0.6 Log P cut-off without consideration of solubility is no guarantee of C_{\max} improvement. Those systems that show a C_{\max} ratio of less than 1 (less bioavailable than the parent API) are those which had been seen to show decreases in solubility or only modest solubility increases in Figure 25. It should also be noted that only 13.5% of the data points sit outside of the ' ± 0.6 Log P zone and this highlights the main drawback to this analysis. A comparable dataset has previously been compiled and analysed by Shan *et al.*, [175] with new studies added in the work presented here. Shan noted that the literature is still very sparse in this area, with significant numbers of the same carboxylic acids used to form cocrystals of mostly BCS class II drugs, so conclusions drawn from this data may not be able to be robustly applied across the broader spectrum of API chemistry and ionic cocrystals.

3.9 Future questions for pharmacokinetic design

A number of studies have looked at the impact of absorption processes when using cocrystals, but there have been two studies[172, 188] in which the cocrystal significantly alters the clearance rate of the parent API molecule, these were in quercetin and AMG 517 respectively. Most small molecule drugs are cleared from the body by first order processes (elimination half-life remains constant), [166] so seeing a significant alteration in this parameter is an unusual occurrence. Within the reported quercetin cocrystals[188] it was seen that changing the coformer from caffeine to theobromine led to an increase in the clearance half-life of the API from 26 minutes to 145 minutes (~ 80% increase). In AMG 517[172] increasing the dose of the sorbic acid cocrystal from 10 mg to 500 mg led to a staged increase in the clearance rate from 16.5 hours to 23.1 hours (~30% increase). In both cases the cocrystals led to increased drug absorption, so it is possible that the increase in the total concentration in the body has saturated the clearance route in these systems, moving the process away from first order and increasing the clearance half-life. It is also possible however that the variation in coformer used, or the increase in the *in vivo* concentration of the same coformer (respectively), led to some degree of liver enzyme inhibition and resulted in longer clearance half-lives. As it is considered normal for the coformer and API to be independent by the time that clearance processes are occurring it is clear from this evidence that some consideration is needed to the enzyme inhibition status of the coformer in the design of cocrystals. Consideration of the inhibitor status of cofomers is pertinent both from the perspective of elimination processes, as discussed here, but also absorption processes. This is because there are a number of active cytochrome P450 enzymes in the gut wall[195] which may be inhibited and lead to increased systemic concentrations of the active drug as it is not metabolised in the gut wall. There is clear evidence that some common cofomers, for example caffeine and vanillin, actively lead to inhibition of the cytochrome P450 system.[196] In this respect the practice of dosing a physical mixture of the coformer and API[179, 181, 189] as well as the cocrystal appears prudent, although from the small data set it is uncertain whether the coformer being dosed outside the cocrystal affects the absorption of the coformer as well as that of the API. Based on this evidence it would seem advisable when developing PK studies for higher animal species, if possible to develop a suitable assay, to track the coformer's pharmacokinetic profile and any inhibition effects it may exert. When selecting the final API form considering the

additional medicines that a patient is likely to be taking may also avoid the potential of inducing unwanted interactions with other therapies.

4. Conclusions

From the data which has been examined it is clear that cocrystals can be designed for use in pharmaceutical products and can be applied along with salts as part of the form selection toolbox. Cocrystals and salts offer a viable method for the improvement of *in vivo* exposure for poorly soluble API molecules, as well as a route to alter their physical behaviours. Consideration of the following physicochemical parameters is essential for the effective design of functional cocrystal and salt forms: intrinsic solubility of the API, lipophilicity of both components (in the form of Log *P*) and the pK_a of both components to assure phase stability. Melting point and glass transition temperature are important considerations when contemplating manufacturing routes, but fluctuations up and down in temperature (from the melting points of the parent phases) have been seen in cocrystal phases. Further to this development approaches which consider the end user (i.e. the patient) at the start of the discovery/development cycle are advisable in order to determine effective production routes and the potential of drug A to drug B-coformer interactions as early as possible.

5. References

- [1] S.M. Berge, L.D. Bighley, D.C. Monkhouse, Pharmaceutical salts, *Journal of Pharmaceutical Sciences*, 66 (1977) 1-19.
- [2] Ö. Almarsson, M.L. Peterson, M. Zaworotko, The A to Z of pharmaceutical cocrystals: a decade of fast-moving new science and patents, *Pharmaceutical patent analyst*, 1 (2012) 313-327.
- [3] Ö. Almarsson, M.J. Zaworotko, Crystal engineering of the composition of pharmaceutical phases. Do pharmaceutical co-crystals represent a new path to improved medicines?, *Chemical communications*, (2004) 1889-1896.
- [4] C.B. Aakeröy, D.J. Salmon, Building co-crystals with molecular sense and supramolecular sensibility, *CrystEngComm*, 7 (2005) 439-448.
- [5] A.V. Trask, W.D.S. Motherwell, W. Jones, Pharmaceutical Cocrystallization: Engineering a Remedy for Caffeine Hydration, *Crystal Growth & Design*, 5 (2005) 1013-1021.
- [6] P. Vishweshwar, J.A. McMahon, J.A. Bis, M.J. Zaworotko, Pharmaceutical co-crystals, *Journal of Pharmaceutical Sciences*, 95 (2006) 499-516.
- [7] S.L. Morissette, Ö. Almarsson, M.L. Peterson, J.F. Remenar, M.J. Read, A.V. Lemmo, S. Ellis, M.J. Cima, C.R. Gardner, High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids, *Advanced drug delivery reviews*, 56 (2004) 275-300.
- [8] N. Rodríguez-Hornedo, Cocrystals: Molecular design of pharmaceutical materials, *Molecular Pharmaceutics*, 4 (2007) 299-300.
- [9] N. Blagden, D.J. Berry, A. Parkin, H. Javed, A. Ibrahim, P.T. Gavan, L.L. De Matos, C.C. Seaton, Current directions in co-crystal growth, *New Journal of Chemistry*, 32 (2008) 1659-1672.
- [10] S. Ross, D.A. Lamprou, D. Douroumis, Engineering and manufacturing of pharmaceutical co-crystals: A review on solvent-free manufacturing technologies, *Chemical Communications*, (2016).
- [11] N. Blagden, M. de Matas, P.T. Gavan, P. York, Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates, *Advanced Drug Delivery Reviews*, 59 (2007) 617-630.
- [12] N. Schultheiss, A. Newman, Pharmaceutical Cocrystals and Their Physicochemical Properties, *Cryst. Growth Des.*, 9 (2009) 2950-2967.
- [13] G. Bolla, A. Nangia, Pharmaceutical cocrystals: walking the talk, *Chem. Commun. (Cambridge, U. K.)*, 52 (2016) 8342-8360.
- [14] N.K. Duggirala, M.L. Perry, O. Almarsson, M.J. Zaworotko, Pharmaceutical cocrystals: along the path to improved medicines, *Chemical Communications*, 52 (2016) 640-655.
- [15] U.S.D.o.H.a.H. Services, F.a.D. Administration, C.f.D.E.a.R. (CDER), Regulatory Classification of Pharmaceutical Co-Crystals Guidance for Industry, FDA, 2016.
- [16] EMA, Reflection paper on the use of cocrystals and other solid 5 state forms of active substances in medicinal products, 2014.
- [17] A.V. Trask, An Overview of Pharmaceutical Cocrystals as Intellectual Property, *Molecular Pharmaceutics*, 4 (2007) 301-309.
- [18] S.L. Childs, G.P. Stahly, A. Park, The Salt–Cocrystal Continuum: The Influence of Crystal Structure on Ionization State, *Molecular Pharmaceutics*, 4 (2007) 323-338.
- [19] E. Grothe, H. Meekes, E. Vlieg, J.H. ter Horst, R. de Gelder, Solvates, Salts, and Cocrystals: A Proposal for a Feasible Classification System, *Crystal Growth & Design*, 16 (2016) 3237-3243.
- [20] S.L. Price, Predicting crystal structures of organic compounds, *Chemical Society Reviews*, 43 (2014) 2098-2111.
- [21] A.M. Reilly, R.I. Cooper, C.S. Adjiman, S. Bhattacharya, A.D. Boese, J.G. Brandenburg, P.J. Bygrave, R. Bylsma, J.E. Campbell, R. Car, D.H. Case, R. Chadha, J.C. Cole, K. Cosburn, H.M. Cuppen, F. Curtis, G.M. Day, R.A. DiStasio Jr, A. Dzyabchenko, B.P. van Eijck, D.M. Elking, J.A. van den Ende, J.C. Facelli, M.B. Ferraro, L. Fusti-Molnar, C.-A. Gatsiou, T.S. Gee, R. de Gelder, L.M. Ghiringhelli, H. Goto, S. Grimme, R. Guo, D.W.M. Hofmann, J. Hoja, R.K. Hylton, L. Iuzzolino, W. Jankiewicz, D.T. de Jong, J. Kendrick, N.J.J. de Klerk, H.-Y. Ko, L.N. Kuleshova, X. Li, S. Lohani, F.J.J. Leusen, A.M. Lund, J. Lv, Y. Ma, N. Marom, A.E. Masunov, P. McCabe, D.P. McMahon, H. Meekes, M.P. Metz, A.J. Misquitta, S.

- Mohamed, B. Monserrat, R.J. Needs, M.A. Neumann, J. Nyman, S. Obata, H. Oberhofer, A.R. Oganov, A.M. Orendt, G.I. Pagola, C.C. Pantelides, C.J. Pickard, R. Podeszwa, L.S. Price, S.L. Price, A. Pulido, M.G. Read, K. Reuter, E. Schneider, C. Schober, G.P. Shields, P. Singh, I.J. Sugden, K. Szalewicz, C.R. Taylor, A. Tkatchenko, M.E. Tuckerman, F. Vacarro, M. Vasileiadis, A. Vazquez-Mayagoitia, L. Vogt, Y. Wang, R.E. Watson, G.A. de Wijs, J. Yang, Q. Zhu, C.R. Groom, Report on the sixth blind test of organic crystal structure prediction methods, *Acta Crystallogr. Sect. B*, 72 (2016) 439-459.
- [22] A.J. Cruz Cabeza, G.M. Day, W.D.S. Motherwell, W. Jones, Prediction and Observation of Isostructurality Induced by Solvent Incorporation in Multicomponent Crystals, *J. Am. Chem. Soc.*, 128 (2006) 14466-14467.
- [23] M.C. Etter, Encoding and Decoding Hydrogen Bond Patterns of Organic Compounds, *Acc. Chem. Res.*, 23 (1990) 120-126.
- [24] C.P. Brock, J.D. Dunitz, Towards a Grammar of Crystal Packing, *Chem. Mater.*, 6 (1994) 1118 - 1127.
- [25] C.P. Brock, Systematic Study of Crystal Packing, in: J.A.K. Howard (Ed.) *Implications of Molecular and Materials Structure for New Technologies*, Kluwer, Dordrecht, 1999, pp. 251-262.
- [26] C.B. Aakeröy, A.M. Beatty, B.A. Helfrich, "Total Synthesis" Supramolecular Style: Design and Hydrogen-Bond-Directed Assembly of Ternary Supramolecules, *Angew. Chem., Int. Ed.*, 40 (2001) 3240-3242.
- [27] D.A. Adsmond, A.S. Sinha, U.B.R. Khandavilli, A.R. Maguire, S.E. Lawrence, Design and Synthesis of Ternary Cocrystals Using Carboxyphenols and Two Complementary Acceptor Compounds, *Cryst. Growth Des.*, 16 (2016) 59-69.
- [28] G.R. Desiraju, Supramolecular Synthons in Crystal Engineering - a New Organic- Synthesis, *Angew. Chem., Int. Ed. Engl.*, 34 (1995) 2311-2327.
- [29] F.H. Allen, W.D.S. Motherwell, P.R. Raithby, G.P. Shields, R. Taylor, Systematic analysis of the probabilities of formation of bimolecular hydrogen-bonded ring motifs in organic crystal structures, *New J. Chem.*, 23 (1999) 25-34.
- [30] B. Swapna, D. Maddileti, A. Nangia, Cocrystals of the Tuberculosis Drug Isoniazid: Polymorphism, Isostructurality, and Stability, *Cryst. Growth Des.*, 14 (2014) 5991-6005.
- [31] D.P. McNamara, S.L. Childs, J. Giordano, A. Iarricco, J. Cassidy, M.S. Shet, R. Mannion, E. O'Donnell, A. Park, Use of a Glutaric Acid Cocrystal to Improve Oral Bioavailability of a Low Solubility API, *Pharmaceutical Research*, 23 (2006) 1888-1897.
- [32] S. Mohamed, D.A. Tocher, S.L. Price, Computational prediction of salt and cocrystal structures- Does a proton position matter?, *Int. J. Pharm.*, 418 (2011) 187-198.
- [33] F. Allen, The Cambridge Structural Database: a quarter of a million crystal structures and rising, *Acta Crystallographica Section B*, 58 (2002) 380-388.
- [34] J.A. Bis, P. Vishweshwar, D. Weyna, M.J. Zaworotko, Hierarchy of supramolecular synthons: Persistent hydroxyl...pyridine hydrogen bonds in cocrystals that contain a cyano acceptor, *Molecular Pharmaceutics*, 4 (2007) 401-416.
- [35] C.B. Aakeröy, A. Rajbanshi, Z.J. Li, J. Desper, Mapping out the synthetic landscape for re-crystallization, co-crystallization and salt formation, *CrystEngComm*, 12 (2010) 4231-4239.
- [36] W.-Q.T. Tong, G. Whitesell, In Situ Salt Screening-A Useful Technique for Discovery Support and Preformulation Studies, *Pharmaceutical Development and Technology*, 3 (1998) 215-223.
- [37] S.M. Pratik, A. Datta, Nonequimolar Mixture of Organic Acids and Bases: An Exception to the Rule of Thumb for Salt or Cocrystal, *The Journal of Physical Chemistry B*, 120 (2016) 7606-7613.
- [38] R. Lee, A.J. Firbank, M.R. Probert, J.W. Steed, Expanding the Pyridine-Formic Acid Cocrystal Landscape under Extreme Conditions, *Cryst. Growth Des.*, 16 (2016) 4005-4011.
- [39] V.V. Chernyshev, S.V. Pirogov, I.N. Shishkina, Y.A. Velikodny, Monoclinic form I of clopidogrel hydrogen sulfate from powder diffraction data, *Acta Crystallographica Section E*, 66 (2010) o2101-o2102.
- [40] B.C.R. Sansam, K.M. Anderson, J.W. Steed, A Simple Strategy for Crystal Engineering Water Clusters, *Cryst. Growth. Des.*, 7 (2007) 2649-2653.

- [41] P.T. Muthiah, B. Umadevi, N. Stanley, X. Shui, D.S. Eggleston, Hydrogen bonding patterns in trimethoprim sulfate trihydrate [trimethoprim = 2,4-diamino-5-(3,4,5-methoxybenzyl)pyrimidine], *Acta Crystallographica Section E*, 57 (2001) o1179-o1182.
- [42] K. Fücke, J.W. Steed, X-ray and Neutron Diffraction in the Study of Organic Crystalline Hydrates, *Water*, 2 (2010) 333-350.
- [43] R.K. Khankari, D.J.W. Grant, Pharmaceutical hydrates, *Thermochimica Acta*, 248 (1995) 61-79.
- [44] A.F. Wells, *Structural Inorganic Chemistry*, Clarendon Press, Oxford, 1962, pp. 572-600.
- [45] J. Skieneh, B. Khalili Najafabadi, S. Horne, S. Rohani, Crystallization of Esomeprazole Magnesium Water/Butanol Solvate, *Molecules*, 21 (2016) 544.
- [46] D. White, R.R. Whittle, G.W. Stowell, L.B. Whittall, *MAGNESIUM COMPLEXES OF S-OMEPRAZOLE*, aaiPharma, Inc., US, 2005.
- [47] N.J. Babu, P. Sanphui, A. Nangia, Crystal Engineering of Stable Temozolomide Cocrystals, *Chemistry – An Asian Journal*, 7 (2012) 2274-2285.
- [48] C.B. Aakeröy, M.E. Fasulo, J. Desper, Cocrystal or salt: Does it really matter?, *Molecular Pharmaceutics*, 4 (2007) 317-322.
- [49] C.C. Wilson, Migration of the proton in the strong O-H center dot center dot center dot O hydrogen bond in urea-phosphoric acid (1/1), *Acta Crystallogr. Sect. B*, 57 (2001) 435-439.
- [50] A.J. Kesel, I. Sonnenbichler, K. Polborn, L. Gürtler, W.E.F. Klinkert, M. Modolell, A.K. Nüssler, W. Oberthür, A new antioxidative vitamin B6 analogue modulates pathophysiological cell proliferation and damage, *Bioorg. & Med. Chem.*, 7 (1999) 359-367.
- [51] P.M. Dean, J. Turanjanin, M. Yoshizawa-Fujita, D.R. MacFarlane, J.L. Scott, Exploring an Anti-Crystal Engineering Approach to the Preparation of Pharmaceutically Active Ionic Liquids, *Cryst. Growth Des.*, 9 (2009) 1137-1145.
- [52] P. Forgacs, J. Provost, A. Touche, D. Guenard, C. Thal, J. Guilhem, Structures de l'odyendane et l'odyendene deux nouveaux quassinoides d'odyendea gabonensis (pierre) engl. Simaroubacees, *Tetrahedron Lett.*, 26 (1985) 3457-3460.
- [53] M.R. Chierotti, R. Gobetto, NMR crystallography: the use of dipolar interactions in polymorph and co-crystal investigation, *CrystEngComm*, 15 (2013) 8599-8612.
- [54] A. Jayasankar, L.S. Reddy, S.J. Bethune, N. Rodríguez-Hornedo, Role of Cocrystal and Solution Chemistry on the Formation and Stability of Cocrystals with Different Stoichiometry, *Cryst. Growth Des.*, 9 (2009) 889-897.
- [55] N. Variankaval, R. Wenslow, J. Murry, R. Hartman, R. Helmy, E. Kwong, S.-D. Clas, C. Dalton, I. Santos, Preparation and Solid-State Characterization of Nonstoichiometric Cocrystals of a Phosphodiesterase-IV Inhibitor and L-Tartaric Acid, *Crystal Growth & Design*, 6 (2006) 690-700.
- [56] D.-K. Bucar, G.M. Day, I. Halasz, G.G.Z. Zhang, J.R.G. Sander, D.G. Reid, L.R. MacGillivray, M.J. Duer, W. Jones, The curious case of (caffeine)[middle dot](benzoic acid): how heteronuclear seeding allowed the formation of an elusive cocrystal, *Chemical Science*, 4 (2013) 4417-4425.
- [57] J.H. Williams, The molecular electric quadrupole moment and solid-state architecture, *Acc. Chem. Res.*, 26 (1993) 593-598.
- [58] C. J. Aspley, C. Boxwell, M. L. Buil, C. L. Higgitt, R. N. Perutz, C. Long, A new combination of donor and acceptor: bis([small eta]6-benzene)chromium and hexafluorobenzene form a charge-transfer stacked crystal, *Chem. Commun.*, (1999) 1027-1028.
- [59] J.C. Ma, D.A. Dougherty, The cation-pi interaction, *Chem. Rev.*, 97 (1997) 1303-1324.
- [60] B.L. Schottel, H.T. Chifotides, K.R. Dunbar, Anion-pi interactions, *Chem. Soc. Rev.*, 37 (2008) 68-83.
- [61] J.M. Harrowfield, M.I. Ogden, W.R. Richmond, A.H. White, Calixarene-Cupped Cesium - a Coordination Conundrum, *J. Chem. Soc.-Chem. Commun.*, (1991) 1159-1161.
- [62] G. Cavallo, P. Metrangolo, R. Milani, T. Pilati, A. Priimagi, G. Resnati, G. Terraneo, The halogen bond, *Chemical reviews*, 116 (2016) 2478-2601.
- [63] W. Fleischer, K. Reimer, Povidone-Iodine in Antisepsis – State of the Art, *Dermatology*, 195(suppl 2) (1997) 3-9.

- [64] M. Baldrighi, G. Cavallo, M.R. Chierotti, R. Gobetto, P. Metrangolo, T. Pilati, G. Resnati, G. Terraneo, Halogen Bonding and Pharmaceutical Cocrystals: The Case of a Widely Used Preservative, *Molecular Pharmaceutics*, 10 (2013) 1760-1772.
- [65] D. Cincic, T. Friščić, W. Jones, A stepwise mechanism for the mechanochemical synthesis of halogen-bonded cocrystal architectures, *J. Am. Chem. Soc.*, 130 (2008) 7524-7525.
- [66] L. Meazza, J.A. Foster, K. Fucke, P. Metrangolo, G. Resnati, J.W. Steed, Halogen-bonding-triggered supramolecular gel formation, *Nature Chem.*, 5 (2013) 42-47.
- [67] H. Schmidbaur, A. Schier, Auophilic interactions as a subject of current research: an up-date, *Chemical Society Reviews*, 41 (2012) 370-412.
- [68] W. Dong, Y.-Q. Sun, B. Yu, H.-B. Zhou, H.-B. Song, Z.-Q. Liu, Q.-M. Wang, D.-Z. Liao, Z.-H. Jiang, S.-P. Yan, P. Cheng, Synthesis, crystal structures and luminescent properties of two supramolecular assemblies containing [Au(CN)₂]⁻ building block, *New J. Chem.*, 28 (2004) 1347-1351.
- [69] A.G. Orpen, Secondary Bonding as a Potential Design Tool for Crystal Engineering, in: D. Braga, F. Grepioni, A.G. Orpen (Eds.) *Crystal Engineering: From Molecules and Crystals to Materials*, Springer Netherlands, Dordrecht, 1999, pp. 107-127.
- [70] N.W. Alcock, W.D. Harrison, SECONDARY BONDING .8. THE CRYSTAL AND MOLECULAR-STRUCTURE OF DIPHENYL TELLUROXIDE, *J. Chem. Soc., Dalton Trans.*, (1982) 709-712.
- [71] F. Katzsch, T. Gruber, E. Weber, Crystalline Inclusion of Wheel-and-Axle Diol Hosts Featuring Benzo[b]thiophene Units as a Lateral Construction Element, *Cryst. Growth Des.*, 15 (2015) 5047-5061.
- [72] G.D. Andreetti, R. Ungaro, A. Pochini, Crystal and molecular structure of cyclo{quarter[(5-*t*-butyl-2-hydroxy-1,3-phenylene)methylene]} toluene (1:1) clathrate, *J. Chem. Soc., Chem. Commun.*, (1979) 1005-1007.
- [73] A.I. Kitaigorodskii, *Organic Chemical Crystallography*, Iliffe, London, 1962.
- [74] K.M. Steed, J.W. Steed, Packing Problems: High Z' Crystal Structures and Their Relationship to Cocrystals, Inclusion Compounds, and Polymorphism, *Chemical Reviews*, 115 (2015) 2895-2933.
- [75] F.H. Herbstein, R.E. Marsh, Trimesic acid hydrate, *Acta Crystallogr., Sect. B*, 33 (1977) 2358.
- [76] F.H. Herbstein, R.E. Marsh, Crystal-Structures of Trimesic Acid, Its Hydrates and Complexes .2. Trimesic Acid Monohydrate-2/9 Picric Acid and Trimesic Acid 5/6 Hydrate, *Acta Crystallogr. Sect. B*, 33 (1977) 2358-2367.
- [77] B.F. Broberg, H.C. Evers, Local anesthetic mixture for topical application and method for obtaining local anesthesia, Google Patents, 1985.
- [78] S. Cherukuvada, A. Nangia, Eutectics as improved pharmaceutical materials: design, properties and characterization, *Chemical Communications*, 50 (2014) 906-923.
- [79] P.H. Karpinski, Polymorphism of active pharmaceutical ingredients, *Chemical engineering & technology*, 29 (2006) 233-237.
- [80] E. Lu, N. Rodríguez-Hornedo, R. Suryanarayanan, A rapid thermal method for cocrystal screening, *CrystEngComm*, 10 (2008) 665-668.
- [81] D.J. Berry, C.C. Seaton, W. Clegg, R.W. Harrington, S.J. Coles, P.N. Horton, M.B. Hursthouse, R. Storey, W. Jones, T. Friscic, Applying hot-stage microscopy to co-crystal screening: a study of nicotinamide with seven active pharmaceutical ingredients, *Crystal Growth and Design*, 8 (2008) 1697-1712.
- [82] A.T.M. Serajuddin, Salt formation to improve drug solubility, *Advanced Drug Delivery Reviews*, 59 (2007) 603-616.
- [83] A. Avdeef, Solubility of sparingly-soluble ionizable drugs, *Advanced Drug Delivery Reviews*, 59 (2007) 568-590.
- [84] H.G. Brittain, Strategy for the Prediction and Selection of Drug Substance Salt Forms, *Pharmaceutical Technology*, 31 (2007) 78-88.
- [85] G.A. Stephenson, A. Aburub, T.A. Woods, Physical stability of salts of weak bases in the solid-state, *Journal of Pharmaceutical Sciences*, 100 (2011) 1607-1617.

- [86] S. Paulekuhn, Formation and analysis of pharmaceutical salts of difficultly soluble, weakly basic active substances, 2011, pp. No pp.
- [87] S.J. Bethune, N. Huang, A. Jayasankar, N. Rodríguez-Hornedo, Understanding and Predicting the Effect of Cocrystal Components and pH on Cocrystal Solubility, *Crystal Growth & Design*, 9 (2009) 3976-3988.
- [88] W.-Q.T. Tong, G. Whitesell, In situ salt screening-a useful technique for discovery support and preformulation studies, *Pharmaceutical development and technology*, (2008).
- [89] C. Saal, A. Becker, Pharmaceutical salts: A summary on doses of salt formers from the Orange Book, *Eur. J. Pharm. Sci.*, 49 (2013) 614-623.
- [90] P.H. Stahl, C.G. Wermuth, *Handbook of Pharmaceutical salts properties, selection, and use*, John Wiley & Sons 2008.
- [91] J.B. Bogardus, R.K. Blackwood, Solubility of Doxycycline in Aqueous Solution, *Journal of Pharmaceutical Sciences*, 68 (1979) 188-194.
- [92] P. Guerrieri, L.S. Taylor, Role of Salt and Excipient Properties on Disproportionation in the Solid-State, *Pharmaceutical Research*, 26 (2009) 2015-2026.
- [93] P.P. Guerrieri, Investigation of the fundamental basis of hygroscopicity in pharmaceutical salts and the consequent impact on physical and chemical stability, 2009, pp. 235 pp.
- [94] D.J. Good, N. Rodríguez-Hornedo, Solubility Advantage of Pharmaceutical Cocrystals, *Crystal Growth & Design*, 9 (2009) 2252-2264.
- [95] M.P. Lipert, L. Roy, S.L. Childs, N. Rodríguez-Hornedo, Cocrystal Solubilization in Biorelevant Media and its Prediction from Drug Solubilization, *Journal of Pharmaceutical Sciences*, 104 (2015) 4153-4163.
- [96] R. Thakuria, A. Delori, W. Jones, M.P. Lipert, L. Roy, N. Rodriguez-Hornedo, Pharmaceutical cocrystals and poorly soluble drugs, *International journal of pharmaceutics*, 453 (2013) 101-125.
- [97] G. Kuminek, F. Cao, A. Bahia de Oliveira da Rocha, S. Goncalves Cardoso, N. Rodriguez-Hornedo, Cocrystals to facilitate delivery of poorly soluble compounds beyond-rule-of-5, *Adv. Drug Delivery Rev.*, 101 (2016) 143-166.
- [98] G. Kuminek, F. Cao, A. Bahia de Oliveira da Rocha, S. Gonçalves Cardoso, N. Rodríguez-Hornedo, Cocrystals to facilitate delivery of poorly soluble compounds beyond-rule-of-5, *Advanced Drug Delivery Reviews*, 101 (2016) 143-166.
- [99] N. Issa, P.G. Karamertzanis, G.W.A. Welch, S.L. Price, Can the Formation of Pharmaceutical Cocrystals Be Computationally Predicted? I. Comparison of Lattice Energies, *Crystal Growth & Design*, 9 (2009) 442-453.
- [100] H.S. Chan, J. Kendrick, M.A. Neumann, F.J. Leusen, Towards ab initio screening of co-crystal formation through lattice energy calculations and crystal structure prediction of nicotinamide, isonicotinamide, picolinamide and paracetamol multi-component crystals, *CrystEngComm*, 15 (2013) 3799-3807.
- [101] A.M. Reilly, R.I. Cooper, C.S. Adjiman, S. Bhattacharya, A.D. Boese, J.G. Brandenburg, P.J. Bygrave, R. Bylsma, J.E. Campbell, R. Car, Report on the sixth blind test of organic crystal-structure prediction methods, *Acta Crystallographica Section B*, (2016) 1-59.
- [102] D. Musumeci, C.A. Hunter, R. Prohens, S. Scuderi, J.F. McCabe, Virtual cocrystal screening, *Chemical Science*, 2 (2011) 883-890.
- [103] T. Grecu, C.A. Hunter, E.J. Gardiner, J.F. McCabe, Validation of a computational cocrystal prediction tool: comparison of virtual and experimental cocrystal screening results, *Crystal Growth & Design*, 14 (2013) 165-171.
- [104] Y.A. Abramov, C. Loschen, A. Klamt, Rational Coformer or Solvent Selection for Pharmaceutical Cocrystallization or Desolvation, *Journal of Pharmaceutical Sciences*, 101 3687-3697.
- [105] C. Loschen, A. Klamt, Solubility prediction, solvate and cocrystal screening as tools for rational crystal engineering, *J. Pharm. Pharmacol.*, 67 (2015) 803-811.
- [106] L. Fábán, Cambridge Structural Database Analysis of Molecular Complementarity in Cocrystals, *Crystal Growth & Design*, 9 (2009) 1436-1443.

- [107] A. Gavezzotti, V. Colombo, L. Lo Presti, Facts and Factors in the Formation and Stability of Binary Crystals, *Crystal Growth & Design*, (2016).
- [108] S.J. Nehm, B. Rodríguez-Spong, N. Rodríguez-Hornedo, Phase Solubility Diagrams of Cocrystals Are Explained by Solubility Product and Solution Complexation, *Crystal Growth & Design*, 6 (2006) 592-600.
- [109] S.L. Childs, L.J. Chyall, J.T. Dunlap, V.N. Smolenskaya, B.C. Stahly, G.P. Stahly, Crystal Engineering Approach To Forming Cocrystals of Amine Hydrochlorides with Organic Acids. Molecular Complexes of Fluoxetine Hydrochloride with Benzoic, Succinic, and Fumaric Acids, *Journal of the American Chemical Society*, 126 (2004) 13335-13342.
- [110] R.A. Chiarella, R.J. Davey, M.L. Peterson, Making Co-Crystals The Utility of Ternary Phase Diagrams, *Crystal Growth & Design*, 7 (2007) 1223-1226.
- [111] C.L. Cooke, R.J. Davey, S. Black, C. Muryn, R.G. Pritchard, Binary and Ternary Phase Diagrams as Routes to Salt Discovery: Ephedrine and Pimelic Acid, *Crystal Growth & Design*, 10 (2010) 5270-5278.
- [112] D.M. Croker, R.J. Davey, Å.C. Rasmuson, C.C. Seaton, Nucleation in the p-Toluenesulfonamide/Triphenylphosphine Oxide Co-crystal System, *Crystal Growth & Design*, 13 (2013) 3754-3762.
- [113] A. Ainouz, J.-R. Authelin, P. Billot, H. Lieberman, Modeling and prediction of cocrystal phase diagrams, *International journal of pharmaceuticals*, 374 (2009) 82-89.
- [114] J.L. Cook, C.A. Hunter, C.M.R. Low, A. Perez-Velasco, J.G. Vinter, Solvent Effects on Hydrogen Bonding, *Angewandte Chemie International Edition*, 46 (2007) 3706-3709.
- [115] K. Fücke, S.A. Myz, T.P. Shakhtshneider, E.V. Boldyreva, U.J. Griesser, How good are the crystallisation methods for co-crystals? A comparative study of piroxicam, *New Journal of Chemistry*, 36 (2012) 1969-1977.
- [116] T. Friščić, W. Jones, Recent Advances in Understanding the Mechanism of Cocrystal Formation via Grinding, *Crystal Growth & Design*, 9 (2009) 1621-1637.
- [117] A. Delori, T. Friščić, W. Jones, The role of mechanochemistry and supramolecular design in the development of pharmaceutical materials, *CrystEngComm*, 14 (2012) 2350-2362.
- [118] L. Lange, G. Sadowski, Thermodynamic Modeling for Efficient Cocrystal Formation, *Cryst. Growth Des.*, 15 (2015) 4406-4416.
- [119] L. Lange, K. Lehmkeper, G. Sadowski, Predicting the Aqueous Solubility of Pharmaceutical Cocrystals As a Function of pH and Temperature, *Cryst. Growth Des.*, 16 (2016) 2726-2740.
- [120] L. Lange, M. Schleinitz, G. Sadowski, Predicting the Effect of pH on Stability and Solubility of Polymorphs, Hydrates, and Cocrystals, *Crystal Growth & Design*, 16 (2016) 4136-4147.
- [121] L. Lange, G. Sadowski, Polymorphs, Hydrates, Cocrystals, and Cocrystal Hydrates: Thermodynamic Modeling of Theophylline Systems, *Cryst. Growth Des.*, 16 (2016) 4439-4449.
- [122] R.S. Dhumal, A.L. Kelly, P. York, P.D. Coates, A. Paradkar, Cocrystalization and Simultaneous Agglomeration Using Hot Melt Extrusion, *Pharmaceutical Research*, 27 (2010) 2725-2733.
- [123] H.G. Moradiya, M.T. Islam, S. Halsey, M. Maniruzzaman, B.Z. Chowdhry, M.J. Snowden, D. Douroumis, Continuous cocrystallisation of carbamazepine and trans-cinnamic acid via melt extrusion processing, *CrystEngComm*, 16 (2014) 3573-3583.
- [124] M.K. Stanton, A. Bak, Physicochemical Properties of Pharmaceutical Co-Crystals: A Case Study of Ten AMG 517 Co-Crystals, *Crystal Growth & Design*, 8 (2008) 3856-3862.
- [125] Y. Chen, L. Li, J. Yao, Y.-Y. Ma, J.-M. Chen, T.-B. Lu, Improving the Solubility and Bioavailability of Apixaban via Apixaban–Oxalic Acid Cocrystal, *Crystal Growth & Design*, 16 (2016) 2923-2930.
- [126] I. Sarcevic, L. Orola, K.P. Nartowski, Y.Z. Khimyak, A.N. Round, L. Fabian, Mechanistic and Kinetic Insight into Spontaneous Cocrystallization of Isoniazid and Benzoic Acid, *Mol. Pharmaceutics*, 12 (2015) 2981-2992.
- [127] K.P. Nartowski, Y.Z. Khimyak, D.J. Berry, Tuning the spontaneous formation kinetics of caffeine : malonic acid co-crystals, *CrystEngComm*, 18 (2016) 2617-2620.
- [128] S. Jain, Mechanical properties of powders for compaction and tableting: an overview, *Pharmaceutical Science & Technology Today*, 2 (1999) 20-31.

- [129] E.N. Hiestand, Dispersion forces and plastic deformation in tablet bond, *Journal of Pharmaceutical Sciences*, 74 (1985) 768-770.
- [130] E.N. Hiestand, Tablet bond. I. a theoretical model, *International journal of pharmaceutics*, 67 (1991) 217-229.
- [131] E.N. Hiestand, D.P. Smith, Tablet bond. II. Experimental check of model, *International journal of pharmaceutics*, 67 (1991) 231-246.
- [132] N. Blagden, S.J. Coles, D.J. Berry, Pharmaceutical co-crystals - are we there yet?, *CrystEngComm*, 16 (2014) 5753-5761.
- [133] C.C. Sun, H. Hou, Improving Mechanical Properties of Caffeine and Methyl Gallate Crystals by Cocrystallization, *Crystal Growth & Design*, 8 (2008) 1575-1579.
- [134] Z. Rahman, C. Agarabi, A.S. Zidan, S.R. Khan, M.A. Khan, Physico-mechanical and Stability Evaluation of Carbamazepine Cocrystal with Nicotinamide, *AAPS PharmSciTech*, 12 (2011) 693-704.
- [135] Z. Rahman, R. Samy, V.A. Sayeed, M.A. Khan, Physicochemical and mechanical properties of carbamazepine cocrystals with saccharin, *Pharmaceutical Development and Technology*, 17 (2012) 457-465.
- [136] N. Blagden, D.J. Berry, A. Parkin, H. Javed, A. Ibrahim, P.T. Gavan, L.L. De Matos, C.C. Seaton, Current directions in co-crystal growth, *New J. Chem.*, 32 (2008) 1659-1672.
- [137] G.R. Krishna, L. Shi, P.P. Bag, C.C. Sun, C.M. Reddy, Correlation among crystal structure, mechanical behavior, and tabletability in the co-crystals of vanillin isomers, *Crystal Growth & Design*, 15 (2015) 1827-1832.
- [138] P. Sanphui, M.K. Mishra, U. Ramamurty, G.R. Desiraju, Tuning Mechanical Properties of Pharmaceutical Crystals with Multicomponent Crystals: Voriconazole as a Case Study, *Molecular Pharmaceutics*, 12 (2015) 889-897.
- [139] S. Chattoraj, L. Shi, C.C. Sun, Understanding the relationship between crystal structure, plasticity and compaction behaviour of theophylline, methyl gallate, and their 1: 1 co-crystal, *CrystEngComm*, 12 (2010) 2466-2472.
- [140] S. Ghosh, C.M. Reddy, Elastic and Bendable Caffeine Cocrystals: Implications for the Design of Flexible Organic Materials, *Angewandte Chemie International Edition*, 51 (2012) 10319-10323.
- [141] C.-T. Chen, S. Ghosh, C.M. Reddy, M.J. Buehler, Molecular mechanics of elastic and bendable caffeine co-crystals, *Physical Chemistry Chemical Physics*, 16 (2014) 13165-13171.
- [142] B.C. Hancock, M. Parks, What is the True Solubility Advantage for Amorphous Pharmaceuticals?, *Pharmaceutical Research*, 17 (2000) 397-404.
- [143] C. Leuner, J. Dressman, Improving drug solubility for oral delivery using solid dispersions, *European Journal of Pharmaceutics and Biopharmaceutics*, 50 (2000) 47-60.
- [144] T. Vasconcelos, B. Sarmiento, P. Costa, Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs, *Drug discovery today*, 12 (2007) 1068-1075.
- [145] R. Laitinen, K. Löbmann, C.J. Strachan, H. Grohgan, T. Rades, Emerging trends in the stabilization of amorphous drugs, *International journal of pharmaceutics*, 453 (2013) 65-79.
- [146] K.J. Paluch, T. McCabe, H. Müller-Bunz, O.I. Corrigan, A.M. Healy, L. Tajber, Formation and Physicochemical Properties of Crystalline and Amorphous Salts with Different Stoichiometries Formed between Ciprofloxacin and Succinic Acid, *Molecular Pharmaceutics*, 10 (2013) 3640-3654.
- [147] P. Tong, L.S. Taylor, G. Zografi, Influence of Alkali Metal Counterions on the Glass Transition Temperature of Amorphous Indomethacin Salts, *Pharmaceutical Research*, 19 (2002) 649-654.
- [148] V.M. Sonje, L. Kumar, V. Puri, G. Kohli, A.M. Kaushal, A.K. Bansal, Effect of counterions on the properties of amorphous atorvastatin salts, *European Journal of Pharmaceutical Sciences*, 44 (2011) 462-470.
- [149] S.J. Dengale, H. Grohgan, T. Rades, K. Löbmann, Recent advances in co-amorphous drug formulations, *Advanced Drug Delivery Reviews*, 100 (2016) 116-125.
- [150] M. Gordon, J.S. Taylor, Ideal copolymers and the second-order transitions of synthetic rubbers. I. Non-crystalline copolymers, *Journal of Applied Chemistry*, 2 (1952) 493-500.

- [151] K. Löbmann, H. Grohgan, R. Laitinen, C. Strachan, T. Rades, Amino acids as co-amorphous stabilizers for poorly water soluble drugs—Part 1: Preparation, stability and dissolution enhancement, *European Journal of Pharmaceutics and Biopharmaceutics*, 85 (2013) 873-881.
- [152] K. Löbmann, R. Laitinen, C. Strachan, T. Rades, H. Grohgan, Amino acids as co-amorphous stabilizers for poorly water-soluble drugs—Part 2: Molecular interactions, *European Journal of Pharmaceutics and Biopharmaceutics*, 85 (2013) 882-888.
- [153] K.T. Jensen, K. Löbmann, T. Rades, H. Grohgan, Improving co-amorphous drug formulations by the addition of the highly water soluble amino acid, proline, *Pharmaceutics*, 6 (2014) 416-435.
- [154] P.A. Corner, J.J. Harburn, J.W. Steed, J.F. McCabe, D.J. Berry, Stabilisation of an amorphous form of ROY through a predicted co-former interaction, *Chemical Communications*, 52 (2016) 6537-6540.
- [155] B.C. Hancock, G. Zografi, The Relationship Between the Glass Transition Temperature and the Water Content of Amorphous Pharmaceutical Solids, *Pharmaceutical Research*, 11 (1994) 471-477.
- [156] P. Costa, J.M. Sousa Lobo, Modeling and comparison of dissolution profiles, *European Journal of Pharmaceutical Sciences*, 13 (2001) 123-133.
- [157] N.J. Babu, A. Nangia, Solubility Advantage of Amorphous Drugs and Pharmaceutical Cocrystals, *Cryst. Growth Des.*, 11 (2011) 2662-2679.
- [158] G.L. Amidon, H. Lennernäs, V.P. Shah, J.R. Crison, A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability, *Pharmaceutical research*, 12 (1995) 413-420.
- [159] C. Sowa, R.E. Gold, T. Chiodo, R. Vogel, Co-Crystals of Cyprodinil and Dithianon, Google Patents, 2012.
- [160] R. Barbas, F. Martí, R. Prohens, C. Puigjaner, Polymorphism of norfloxacin: Evidence of the enantiotropic relationship between polymorphs A and B, *Crystal growth & design*, 6 (2006) 1463-1467.
- [161] G.O.K. Loh, Y.T.F. Tan, K.K. Peh, Hydrophilic polymer solubilization on norfloxacin solubility in preparation of solid dispersion, *Powder Technology*, 256 (2014) 462-469.
- [162] S. Basavoju, D. Boström, S.P. Velaga, Pharmaceutical Cocrystal and Salts of Norfloxacin, *Crystal Growth & Design*, 6 (2006) 2699-2708.
- [163] M. Pudipeddi, A.T.M. Serajuddin, Trends in Solubility of Polymorphs, *Journal of Pharmaceutical Sciences*, 94 929-939.
- [164] L. Almeida e. Sousa, S.M. Reutzel-Edens, G.A. Stephenson, L.S. Taylor, Supersaturation Potential of Salt, Co-Crystal, and Amorphous Forms of a Model Weak Base, *Cryst. Growth Des.*, 16 (2016) 737-748.
- [165] G.A. Ilevbare, L.S. Taylor, Liquid–Liquid Phase Separation in Highly Supersaturated Aqueous Solutions of Poorly Water-Soluble Drugs: Implications for Solubility Enhancing Formulations, *Crystal Growth & Design*, 13 (2013) 1497-1509.
- [166] S.S. Jambhekar, P.J. Breen, *Basic Pharmacokinetics*, (2009).
- [167] A. Rostami-Hodjegan, G.T. Tucker, Simulation and prediction of in vivo drug metabolism in human populations from in vitro data, *Nat Rev Drug Discov*, 6 (2007) 140-148.
- [168] E.S. Kostewicz, L. Aarons, M. Bergstrand, M.B. Bolger, A. Galetin, O. Hatley, M. Jamei, R. Lloyd, X. Pepin, A. Rostami-Hodjegan, E. Sjögren, C. Tannergren, D.B. Turner, C. Wagner, W. Weitschies, J. Dressman, PBPK models for the prediction of in vivo performance of oral dosage forms, *European Journal of Pharmaceutical Sciences*, 57 (2014) 300-321.
- [169] H.R. Guzmán, M. Tawa, Z. Zhang, P. Ratanabangkoon, P. Shaw, C.R. Gardner, H. Chen, J.P. Moreau, Ö. Almarsson, J.F. Remenar, Combined Use of Crystalline Salt Forms and Precipitation Inhibitors to Improve Oral Absorption of Celecoxib from Solid Oral Formulations, *Journal of Pharmaceutical Sciences*, 96 (2007) 2686-2702.
- [170] A. Bak, A. Gore, E. Yanez, M. Stanton, S. Tufekcic, R. Syed, A. Akrami, M. Rose, S. Surapaneni, T. Bostick, A. King, S. Neervannan, D. Ostovic, A. Koparkar, The co-crystal approach to improve the

- exposure of a water-insoluble compound: AMG 517 sorbic acid co-crystal characterization and pharmacokinetics, *Journal of Pharmaceutical Sciences*, 97 (2008) 3942-3956.
- [171] M.L. Cheney, N. Shan, E.R. Healey, M. Hanna, L. Wojtas, M.J. Zaworotko, V. Sava, S. Song, J.R. Sanchez-Ramos, Effects of Crystal Form on Solubility and Pharmacokinetics: A Crystal Engineering Case Study of Lamotrigine, *Crystal Growth & Design*, 10 (2010) 394-405.
- [172] M.K. Stanton, R.C. Kelly, A. Colletti, M. Langley, E.J. Munson, M.L. Peterson, J. Roberts, M. Wells, Improved pharmacokinetics of AMG 517 through co-crystallization part 2: Analysis of 12 carboxylic acid co-crystals, *Journal of Pharmaceutical Sciences*, 100 (2011) 2734-2743.
- [173] D.R. Weyna, M.L. Cheney, N. Shan, M. Hanna, M.J. Zaworotko, V. Sava, S. Song, J.R. Sanchez-Ramos, Improving Solubility and Pharmacokinetics of Meloxicam via Multiple-Component Crystal Formation, *Molecular Pharmaceutics*, 9 (2012) 2094-2102.
- [174] T. Zhang, Y. Yang, H. Wang, F. Sun, X. Zhao, J. Jia, J. Liu, W. Guo, X. Cui, J. Gu, G. Zhu, Using Dissolution and Pharmacokinetics Studies of Crystal Form to Optimize the Original Iloperidone, *Crystal Growth & Design*, 13 (2013) 5261-5266.
- [175] N. Shan, M.L. Perry, D.R. Weyna, M.J. Zaworotko, Impact of pharmaceutical cocrystals: the effects on drug pharmacokinetics, *Expert Opinion on Drug Metabolism & Toxicology*, 10 (2014) 1255-1271.
- [176] T.-T. Zhang, H.-T. Wang, J.-T. Jia, X.-Q. Cui, Q. Li, G.-S. Zhu, Syntheses and pharmacokinetics properties of an iloperidone pharmaceutical cocrystal, *Inorganic Chemistry Communications*, 39 (2014) 144-146.
- [177] K. Suresh, M.K.C. Mannava, A. Nangia, Cocrystals and alloys of nitazoxanide: enhanced pharmacokinetics, *Chemical Communications*, 52 (2016) 4223-4226.
- [178] J.S. Bhandaru, N. Malothu, R.R. Akkinipally, Characterization and Solubility Studies of Pharmaceutical Cocrystals of Eprosartan Mesylate, *Crystal Growth & Design*, 15 (2015) 1173-1179.
- [179] H. He, Y. Huang, Q. Zhang, J.-R. Wang, X. Mei, Zwitterionic Cocrystals of Flavonoids and Proline: Solid-State Characterization, Pharmaceutical Properties, and Pharmacokinetic Performance, *Crystal Growth & Design*, 16 (2016) 2348-2356.
- [180] S. Ketkar, S.K. Pagire, N.R. Goud, K. Mahadik, A. Nangia, A. Paradkar, Tracing the Architecture of Caffeic Acid Phenethyl Ester Cocrystals: Studies on Crystal Structure, Solubility, and Bioavailability Implications, *Crystal Growth & Design*, (2016).
- [181] Y. Huang, B. Zhang, Y. Gao, J. Zhang, L. Shi, Baicalein–Nicotinamide Cocrystal with Enhanced Solubility, Dissolution, and Oral Bioavailability, *Journal of Pharmaceutical Sciences*, 103 (2014) 2330-2337.
- [182] E. Sravani, M.C. Mannava, D. Kaur, B. Annapurna, R.A. Khan, K. Suresh, S. Mittapalli, A. Nangia, B.D. Kumar, Preclinical bioavailability–bioequivalence and toxico-kinetic profile of stable succinic acid cocrystal of temozolomide, *CURRENT SCIENCE*, 108 (2015) 1097.
- [183] S.L. Childs, P. Kandi, S.R. Lingireddy, Formulation of a Danazol Cocrystal with Controlled Supersaturation Plays an Essential Role in Improving Bioavailability, *Molecular Pharmaceutics*, 10 (2013) 3112-3127.
- [184] A.J. Smith, P. Kavuru, K.K. Arora, S. Kesani, J. Tan, M.J. Zaworotko, R.D. Shytle, Crystal Engineering of Green Tea Epigallocatechin-3-gallate (EGCg) Cocrystals and Pharmacokinetic Modulation in Rats, *Molecular Pharmaceutics*, 10 (2013) 2948-2961.
- [185] P. Sanphui, S. Tothadi, S. Ganguly, G.R. Desiraju, Salt and Cocrystals of Sildenafil with Dicarboxylic Acids: Solubility and Pharmacokinetic Advantage of the Glutarate Salt, *Molecular Pharmaceutics*, 10 (2013) 4687-4697.
- [186] Q. Tao, J.-M. Chen, L. Ma, T.-B. Lu, Phenazopyridine Cocrystal and Salts That Exhibit Enhanced Solubility and Stability, *Crystal Growth & Design*, 12 (2012) 3144-3152.
- [187] R. Chadha, S. Bhandari, J. Haneef, S. Khullar, S. Mandal, Cocrystals of telmisartan: characterization, structure elucidation, in vivo and toxicity studies, *CrystEngComm*, 16 (2014) 8375-8389.

- [188] A.J. Smith, P. Kavuru, L. Wojtas, M.J. Zaworotko, R.D. Shytle, Cocrystals of Quercetin with Improved Solubility and Oral Bioavailability, *Molecular Pharmaceutics*, 8 (2011) 1867-1876.
- [189] M.-S. Jung, J.-S. Kim, M.-S. Kim, A. Alhalaweh, W. Cho, S.-J. Hwang, S.P. Velaga, Bioavailability of indomethacin-saccharin cocrystals, *Journal of Pharmacy and Pharmacology*, 62 (2010) 1560-1568.
- [190] M.L. Cheney, D.R. Weyna, N. Shan, M. Hanna, L. Wojtas, M.J. Zaworotko, Coformer selection in pharmaceutical cocrystal development: A case study of a meloxicam aspirin cocrystal that exhibits enhanced solubility and pharmacokinetics, *Journal of Pharmaceutical Sciences*, 100 (2011) 2172-2181.
- [191] T. Zhang, Y. Yang, X. Zhao, J. Jia, H. Su, H. He, J. Gu, G. Zhu, Dissolution and pharmacokinetic properties of two paliperidone cocrystals with 4-hydroxybenzoic and 4-aminobenzoic acid, *CrystEngComm*, 16 (2014) 7667-7672.
- [192] A. Rohatgi, WebPlotDigitizer, WebPlotDigitizerLocation: Austin, Texas, USA, Version: 3.10.
- [193] Royal Society of Chemistry, ChemSpider, RSC.
- [194] Marvin, ChemAxon, 2013.
- [195] K. Thelen, J.B. Dressman, Cytochrome P450-mediated metabolism in the human gut wall, *Journal of Pharmacy and Pharmacology*, 61 (2009) 541-558.
- [196] K.J. Bamforth, A.L. Jones, R.C. Roberts, M.W.H. Coughtrie, Common food additives are potent inhibitors of human liver 17 α -ethinyloestradiol and dopamine sulphotransferases, *Biochemical Pharmacology*, 46 (1993) 1713-1720.

Graphic abstract

